EXHIBIT 2

Safety considerations for synthetic sling surgery

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Abstract | Implantation of a synthetic midurethral sling (SMUS) is the most commonly performed anti-incontinence operation in women worldwide. The effectiveness of the SMUS is comparable to that of the historical gold standards—autologous fascial slings and the Burch colposuspension. Much controversy, however, has evolved regarding the safety of this type of sling. Overall, the quality of the studies with respect to assessing risks of SMUS-associated complications is currently poor. The most common risks in patients with SMUS include urethral obstruction requiring surgery (2.3% of patients with SMUS), vaginal, bladder and/or urethral erosion requiring surgery (1.8%) and refractory chronic pain (4.1%); these data likely represent the minimum risks. In addition, the failure rate of SMUS implantation surgery is probably at least 5% in patients with stress urinary incontinence (SUI). Furthermore, at least one-third of patients undergoing sling excision surgery develop recurrent SUI. Considering the additional risks of refractory overactive bladder, fistulas and bowel perforations, among others, the overall risk of a negative outcome after SMUS implantation surgery is ≥15%.

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Introduction

The Burch colposuspension and autologous fascial pubovaginal sling have been considered the gold standard treatments of stress (sphincteric) incontinence (SUI), in women since the late 1990s.[1] Historically, pubovaginal slings had been reserved for women with complicated, severe and/or recurrent sphincteric incontinence,[2] but since the late 1990s these have been advocated for treatment of women with all types of sphincteric incontinence—simple and complicated.[3,4] Over the past decade, fueled by a stampede of innovations in synthetic sling composition, structure and implantation techniques and a surge in commercial marketing, implantation of the synthetic midurethral sling (SMUS) has emerged as the most frequently performed operation in women with SUI. Some authors suggest that, to date, over 3 million SMUS implantation procedures have been conducted worldwide, and more than 80% of these happened in the USA.[5] We have been unable to independently verify the number of SMUS implanted worldwide. But, by extrapolating the data from a population-based cohort study,[6] we estimate that approximately 500,000 SMUS were implanted in the USA between years 2001–2010 and that in the ensuing 4 years at least another 300,000 of these procedures were done. Considering the size of the population of the rest of the world and the fact that slings have been implanted *en masse* in most economically developed countries since at least the mid-1990s, a figure of 3 million procedures seems reasonable.[6] Furthermore, in an analysis of 7,200 case logs submitted by American urologists for their certifying credentials in 2013, 83% of operations performed for incontinence in women were SMUS implantations.[7]

SMUS implantation is an operation for the correction of sphincteric incontinence in which a synthetic plastic like mesh strip (the sling) is passed around the urethra into the retropubic space or beneath the urethra through the obturator foramen using trocars. Theoretically, when abdominal pressure rises, as in a cough or sneeze, the urethra is compressed by the sling, and the flow of urine is prevented, much like kinking of a garden hose. The appeal of such procedures is obvious—in theory. SMUS implantation is a minimally invasive, easy-to-perform procedure that is usually completed in under half an hour and, compared to traditional native tissue repairs, enables a much faster recovery with less perioperative morbidity than either the Burch colposuspension or autologous fascial slings. The effectiveness of this approach remains unchallenged. Numerous trials have shown SMUS to be as effective as the autologous fascial sling and Burch colposuspension, with moderate and/or high quality of evidence.[8]

Theory and practice often diverge, though, and this seems to be the case with SMUS. As more SMUS implantations are being performed and the longevity expectations of patients with SMUS are increasing, it has become apparent that unanticipated, serious, sometimes lifestyle-altering complications can occur that are not only unique to patients with SMUS but are also often refractory to treatment.[9,10] The purpose of this Review is to summarize the published literature regarding complications that are uniquely associated with SMUS and to present an overview of complications that are not unique to these slings.

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Competing interests
J.G.B. and V.I. have provided opinions as medicolegal expert witnesses in mesh litigation cases. J.G.B. has acted as a consultant for Astellas Pharma, is a shareholder in P Square Medical, and is a shareholder and co-owns intellectual property with LLC and Symptelligence Medical Informatics. The other authors declare no competing interests.

Key points

- The effectiveness of synthetic midurethral slings (SMUS) is comparable to the time-honoured gold standards—the autologous fascial sling and Burch colposuspension
- At least 15% of women with SMUS experience a serious adverse outcome and/or recurrent sphincteric incontinence
- A subset of women sustain refractory, lifestyle-altering complications that are unique to women with a SMUS
- SMUS-associated complications are under-reported
- The overall quality of the published evidence is currently low with respect to assessing SMUS safety and SMUS-associated complications

Transvaginal mesh slings

The retropubic tension-free transvaginal mesh tape (RP) sling procedure was introduced for treatment of SUI in 1995,[11] and was soon followed in 2001 by the transobturator tape (TOT) sling procedure, in which the sling is introduced via the obturator fossa instead of the retropubic space in an attempt to minimize the complications associated with use of RP slings.[12] Since the introduction of these procedures, results of many modifications of the RP and TOT sling procedures have been published, generally with a follow-up duration of <4 years; most studies had a follow-up duration of ≤1 year.

In a review of prospective randomized controlled trials investigating performance of RP and/or TOT slings, authors reported objective cure rates of patients treated with RP slings ranging between 83.9% and 100%, and 84% and 97.6% for those with TOT slings. Subjective cure rates for patients with RP or TOT slings were 64.5–94% and 60–92.9%, respectively. Median or mean follow-up duration of these studies ranged between 9 months and 24 months.[13] Thus, no notable differences in effectiveness have been revealed by meta-analyses of trials comparing the effectiveness of RP slings with that of TOT slings.[14,15]

More than 19 years have elapsed since the introduction of RP slings and 13 years for TOT slings; results regarding the long-term effectiveness of these treatments are, therefore, now available, with the longest series reporting a follow-up duration of 17 years.[16] Findings of over 200 studies of varying design and quality, investigating the effectiveness of either RP or TOT slings have been published. Of these, only six contain information on outcomes of patients followed up for >5 years and five have reported outcomes after a follow-up duration of 5 years (Table 1). Effectiveness of the treatments tested in these studies has been measured using a variety of subjective and/or objective outcome instruments. Subjective outcomes have been measured using detailed validated questionnaires such as the short urogenital distress inventory (SUDI), short incontinence impact questionnaire, the European quality of life questionnaire,[17] the patient global impression of improvement (PGII) questionnaire,[16,18] the visual/verbal analogue scale (VAS),[16,19–21] non-validated questionnaires[20,22] and telephone surveys.[23] In our judgement, however, the use of some of the validated outcome instruments does not provide sufficiently explicit data to be considered scientifically rigorous. For example, the urogenital distress inventory (UDI)-6 conflates bother with incontinence. This inventory contains the question "Do you experience and how much are you bothered by … leakage,"[24] from stress incontinence? This means a woman could leak only a few drops once a year and have a lot of bother or be totally incontinent and have no bother, yet record exactly the same score. Furthermore, variability in the use of validated and nonvalidated questionnaires might be another explanation of the discrepancies in reported outcomes and can complicate direct comparisons of results from different studies.

A variety of objective outcome instruments have also been used to measure outcomes of these long-term (follow-up duration ≥5 years) studies. The Valsalva stress test, in which the patient is asked to perform a Valsalva manoeuvre to increase abdominal pressure, or the cough test with a full bladder to provocatively test for the development of SUI are the most commonly used objective outcome measures.[17,18,20,21] However, these tests are not standardized and, typically, abdominal and vesical leak point pressures are not measured.[25] Other studies involved checking bladder volume by ultrasonography or just verbally confirming that the patient feels that their bladder is "comfortably full"[26] or "full"[18,27] and then asking the patient to cough. One group asked the patient to do "20 jumping jacks and 3 forceful coughs"[22] or "10 coughs in the standing position"[22] with a 300 ml bladder volume to check for SUI.[22]

The pad-weight test is another objective measurement used to assess treatment outcomes. A variety of pad-weight tests were used in these long-term studies including a 1-hour pad-weight test,[19] a 24-hour pad-weight test[28] and a 48-hour pad-weight test[29] with a result of ≤1 g increase in pad weight defining cure. Two studies used urodynamic evidence of the absence of leak on performing a Valsalva manoeuvre to indicate postoperative success either as a primary endpoint or as an adjunctive measure.[17,18]

Of published series with follow-up durations ≥5 years, the largest consisted of 707 patients and the smallest consisted of 55 patients.[16–23,26,27,29] Overall, objective cure rates of patients with SUI after treatment with either TOT or RP slings at or after a follow-up duration of 5 years ranged between 71% and 92%, and subjective cure rates between 65% and 90.3%. By combining subjective measures of cure and improvement, treatment effectiveness increased from 76% to 95% (Table 1).[16–23,26,27,29]

The series with the longest reported follow-up duration (17 years) was a prospective, single-institution study of 90 women who underwent the (original) RP sling implantation procedures at Uppsala University.[16] The overall rate of subjective cure or improvement assessed using the PGII score was 87% and the objective cure rate assessed using a cough stress test was 91%. Between follow-up years 5 and 17, objective cure rates declined very little—from 94% to 91%—and subjective cure or improvement decreased from 95% to 87%. However, 11 of 53 evaluable patients said that they

Table 1 | Long-term (follow-up duration >5 years) studies of SMUS effectiveness

Study characteristics	Patient characteristics	Mean follow-up duration (months)	Outcome Instrument	Outcomes*
Prospective studies				
Angioli *et al.* (2010)[20] *n*=72	Outcomes of 69 patients with RP or TOT slings were evaluated; 4.1% were lost to follow up	60	ST, NVQ,‡ VAS‡	Objective cure reported in 71% and 73% in patients with RP or TOT slings, respectively; Subjective cure reported by 60% and 62% of patients with RP or TOT slings, respectively
Groutz *et al.* (2011)[23] *n*=60	Outcomes of 52 patients with RP slings were evaluated; 13.3% were lost to follow up	60	NVQ‡	Subjective cure reported by 65% of patients
Groutz *et al.* (2011)[27] *n*=65	Outcomes of 61 patients with TOT slings were evaluated; 6.1% were lost to follow up	60	ST, NVQ‡	Objective cure reported in 74% of patients, 8% had improved symptoms and 18% subjectively reported treatment failure
Cheng *et al.* (2012)[17] *n*=103	Outcomes of 100 patients with TOT slings were evaluated; 2.9% were lost to follow up	65	VUD, QOL,‡ VAS‡	Objective cure reported in 87.4% of patients; subjective cure reported by 78% of patients
Nilsson *et al.* (2013)[16] *n*=90	Outcomes of 58 patients with RP slings were evaluated; 23.3% were lost to follow up	201	ST, VQ‡	Objective cure reported in 91.3% of patients; subjective cure reported by 87%
Serati *et al.* (2013)[18] *n*=191	Outcomes of 185 patients with TOT slings were evaluated; 3.1% were lost to follow up	60	ST, VQ‡	Objective cure reported in 90.3% of patients; subjective cure reported by 90.8%
Svenningsen *et al.* (2013)[22] *n*=603	Outcomes of 483 patients with RP slings were evaluated; 19.9% were lost to follow up	120	Exercise+PT, VQ,‡ NVQ‡	Objective cure reported in 89.9% of patients; subjective cure reported in 76.1% of patients; 18% had improved symptoms; 5.9% had treatment failure
Retrospective studies				
Ankardal *et al.* (2006)[29] *n*=707	Outcomes of 271 patients with RP slings were evaluated; 5.0% were lost to follow up	60§	ST, 48 h PT (NVQ,‡ VAS‡)	Objective cure reported in 83% of patients; subjective cure reported by 73.1% of patients; 15.9% had improved symptoms; 11% had treatment failure
Olsson *et al.* (2010)[21] *n*=147	Outcomes of 104 patients with RP slings were evaluated; 15.6% were lost to follow up	138	ST	Objective cure reported in 84% of patients; subjective cure reported by 77% of patients; 18% had improved symptoms; 5% had treatment failure
Li *et al.* (2012)[19] *n*=55	Outcomes of patients with RP slings were evaluated; percentage of patients lost to follow up not reported	81.85	1 h PT (NVQ‡)	Objective cure reported in 85.5% of patients; subjective cure reported in 74.6% of patients; 7% had improved symptoms; 25.6% had treatment failure
Athanasiou *et al.* (2014)[26] *n*=145	Outcomes of 124 patients with TOT slings were evaluated; 14.4% were lost to follow up	90.3	ST (VQ‡)	Objective cure reported in 81.5% of patients; subjective cure reported in 83.1% of patients; 3.2% had improved symptoms; 13.7% had treatment failure

*Owing to a lack of uniformity in reporting efficacy (improved and failed), improvement and failure were assumed to be based on subjective responses. Incidence of failure was calculated by subtracting the sum of subjective cured and improved responses from 100%. Improved patients were mutually exclusive to cured patients reported. ‡Indicates a subjective outcome instrument. §Indicates actual, not mean follow-up duration. Abbreviations: NVQ, nonvalidated questionnaire; PT, pad-weight test; QOL, quality of life; RP, retropubic tension-free transvaginal mesh tape; SMUS, synthetic midurethral slings; ST, cough or valsalva stress test; TOT, transobturator tape; VAS, visual analogue scale; VQ, validated questionnaire; VUD, videourodynamics.

"experienced leakage during straining".[16] The authors attributed this symptom to the development of severe urge incontinence, which might or might not have been caused by the RP sling itself. However, this study was hindered by the fact that 32 of 90 patients (36%) were not included in the analysis after a follow-up duration of 17 years as 11 (12%) women died, five (6%) had mental impairment and 16 (18%) were lost to follow-up. Overall, 58 (64%) women were available to have their 17-year outcomes evaluated, of whom 46 (51%) women were evaluated in the clinic and 12 (13%) were interviewed by telephone.

By contrast, in another investigation,[30] researchers using much more stringent outcome criteria found the 2-year objective success rate of RP and TOT slings was 77% and 72.3%, respectively and the subjective success rates were 56% and 48%—nearly a 40% reduction in subjective success compared with results from the Uppsala cohort.[16] In this randomized study of 597 patients, objective success was defined as a negative provocative stress test, a negative 24-hour pad-weight test and no need for retreatment of SUI.[27] Subjective success was defined as the absence of self-reported symptoms of SUI on the Medical, Epidemiological and Social Aspects of Aging questionnaire and no urine leakage recorded in a 3-day voiding diary.

The overall effectiveness of RP or TOT slings reported in these long-term studies of patients with SUI has been generally high, although some of the reported success occurred after a secondary operative procedure or medical intervention.[17,19,21,26] Thus, for patients who developed mesh erosion and had successful revision surgery, studies would typically report this as a successful outcome. Secondary treatments for those who develop *de novo* urge incontinence have not been reported, although if the RP or TOT sling procedures are effective in these patients they would typically be included in the 'subjectively cured' or 'improved' category.

The percentage of patients who were lost to follow up should also be carefully noted. In patients who were lost to follow up because of death, the cause of death and

Table 2 | Complications of either RP or TOT slings

Complication	*n*	Complications (% of patients)	Incidence (mean; range)
General complications			
Death within 30 days*	7,762	0 (0.0)	0.0
Urethral obstruction/voiding dysfunction	25,586	1,403 (5.5)	7.3; 0–33.9
Urethral obstruction requiring surgery	9,375	301 (3.2)	2.3; 0–21.3
Urinary infections	13,296	598 (4.5)	7.3; 0–39.1
Pain (within 6 weeks)	5,097	374 (7.3)	7.9; 0–33.3
Neurologic symptoms (within 6 weeks)	1,769	42 (2.4)	1.2; 0–10.3
De novo OAB	14,765	1,512 (10.2)	10.9; 0–48.1
Pelvic organ perforation			
In total	20,630	681 (3.3)	3.5; 0–16.1
Bladder	19,411	579 (3.0)	2.9; 0–16.1
Vaginal	5,521	91 (1.6)	1.4; 0–14.1
Urethral	4,541	6 (0.1)	0.0; 0–1.5
Bowel	3,820	4 (0.1)	0.0; 0–1.7
Ureteral	3,820	1 (0.0)	0.0; 0–1.3
Mesh exposure/erosion/extrusion			
In total	17,520	475 (2.7)	2.5; 0–26.1
Treated conservatively	15,403	112 (0.7)	0.9; 0–7.1
Vaginal	13,496	78 (0.6)	0.7; 0–7.1
Bladder	13,496	5 (0.0)	0.0; 0–5.6
Urethral	13,496	0 (0.0)	0.0
Requiring surgery	16,619	333 (2.0)	1.8; 0–26.1
Vaginal	13,705	235 (1.7)	1.5; 0–15.9
Bladder	13,393	29 (0.2)‡	0.2; 0–15.2
Urethral	13,628	11 (0.1)	0.2; 0–16.7
Longer-term complications			
Refractory pain (>6 weeks)	7,084	247 (3.5)	4.1; 0–30.5
Neurologic Symptoms (>6 weeks)	2,449	51 (2.0)	1.0; 0–10.6
Fistulas	710	2 (0.3)	0.3; 0–1.1

*No deaths were reported in peer-reviewed publications, although 7 were reported in the MAUDE database. ‡Three studies removed from incidence calculation because these were case series of just bladder erosions. Abbreviations: MAUDE, manufacturer and user facility device experience; OAB, overactive bladder; RP, retropubic tension-free transvaginal mesh tape; TOT, transobturator tape.

whether it might have been related to having a TOT or RP sling has not been reported. In addition, long-term studies often featured a lack of follow up in a substantial number of patients. In these long-term studies, between 5% and 36% of patients were either deceased or unavailable for follow up for other reasons (Table 1).

In summary, the long-term effectiveness of RP or TOT slings, as measured by subjective and/or objective instruments suggests that rates of cure or improvement of SUI after implantation are high and compare favourably to the traditional gold standard—the autologous pubovaginal sling. These results might, however, be overly optimistic owing to a host of factors including the suboptimal outcome instruments used, inclusion of patients who might have required multiple procedures and the loss of a substantial number of patients to follow-up monitoring.

SMUS complications

Mesh sling complications can be caused by a host of factors: intraoperative transgressions (such as viscus or vaginal perforation and nerve injury);[31] bacterial contamination;[32] improper tensioning of the sling—either too tight or too loose; host–foreign-body reaction;[33] tissue ingrowth;[34,35] and changes that the mesh undergoes once implanted, such as degradation, curling, banding and leaching of substances into the surrounding tissues (Tables 2–5).[36–38]

Evaluating the incidence, severity and consequences of the various RP and/or TOT sling complications is a daunting task. Of the thousands of published studies, only a few were even designed to track complications in any meaningful way. The short follow-up duration of most of these studies and the lack of accounting for those lost to follow up are additional confounders. In addition, complications might arise that were not even recognized when the original studies were conducted, such as banding as a cause of dyspareunia, which was first described in 2010.[38] Furthermore, all studies are hampered by an absence of the patient's own perception of the severity of the complication. For example, one study[39] that included pain lasting >6 weeks as a category of complication was published, but there is no mention of the severity of this pain, effect on quality of life nor how long the pain actually lasted. For some patients, this pain is treatment-refractory and lifestyle-altering, yet no metric exists that describes this category of complication in sufficient detail. The effects of long-term pain receive no attention at all in any study except for a few case studies of complications.[9,40–44]

The concomitant, widespread use of two different generic sling designs (RP and TOT) with different implantation techniques and at least 41 different commercially available kits,[42] each having different sling and trocar characteristics with potentially different complication profiles, confounds accurate analysis of sling complications. These different characteristics might also portend different complication profiles, yet studies of sling complications almost never distinguish between the different kit types and many do not even separate TOT from RP slings.

Considerable evidence exists that SMUS complications are underreported. Discrepancies exist between the SMUS complication rates reported by urologists from individual institutions, those reported in the literature, the (unreported) experience of tertiary care practices and those in the MAUDE (Manufacturer and User Facility Device Experience) database.[10,40,45] For example, in a population-based cohort of 45 million commercially insured individuals in the USA, investigators found the cumulative risk of requiring sling removal owing to voiding dysfunction or mesh extrusion and/or erosion to be 3.7% (95% CI 3.5–3.9%) after a follow-up duration of 9 years.[6] Furthermore, this study[6] excluded patients whose slings were removed owing to pain and other indications, thus the actual incidence of sling removal owing to complications is probably even higher than that. Extrapolating from this estimate and the estimated number of slings implanted in the

Table 3 | Complications of RP slings

Complication	*n*	Complications (% of patients)	Incidence (mean; range)
General complications			
Death within 30 days	3,499	0 (0.0)	0.0
Urethral obstruction/voiding dysfunction	16,301	704 (2.8)	8.8; 0–32.7
Requiring surgery	6,875	223 (2.4)	2.7; 0–8.9
Urinary infections	8,936	327 (3.7)	8.6; 0–39.1
Pain (within 6 weeks)	2,133	111 (5.2)	4.5; 0–23.1
Neurologic symptoms (within 6 weeks)	520	14 (2.7)	1.6; 0–5.0
De novo OAB	7,989	925 (11.6)	11.4; 0–29.4
Pelvic organ perforation			
In total	13,164	498 (3.8)	4.8; 0–14.3
Bladder	12,929	480 (3.7)	4.6; 0–14.3
Vaginal	763	11 (1.4)	1.0; 0–2.1
Urethral	1,224	4 (0.3)	0.0; 0–1.5
Bowel	800	4 (0.5)	0.0; 0–1.7
Ureteral	800	0 (0.0)	0.0
Mesh exposure/erosion/extrusion			
In total	8,303	179 (2.2)	2.3; 0–26.1
Treated conservatively	7,168	44 (0.6)	0.1; 0–5.6
Vaginal	6,193	22 (0.4)	0.0; 0–4.6
Bladder	6,193	5 (0.1)	0.0; 0–5.6
Urethral	6,193	0 (0.0)	0.0
Requiring surgery	7,902	135 (1.7)	1.6; 0–26.1
Vaginal	6,621	79 (1.2)	1.0; 0–10.9
Bladder	6,386	26 (0.4)	1.4; 0–15.2
Urethral	6,621	4 (0.1)	0.3; 0–16.7
Longer-term complications			
Refractory pain (>6 weeks)	2,328	42 (1.8)	2.0; 0–7.9
Neurologic symptoms (>6 weeks)	908	19 (2.1)	1.0; 0–5.2
Fistulas	388	1 (0.2)	0.4; 0–0.7

Abbreviations: OAB, overactive bladder; RP, retropubic tension-free transvaginal mesh tape.

USA (80% of 3 million slings worldwide),[5] approximately 88,000 removal procedures should have occurred, yet we could find only 740 such procedures that have been reported in peer-reviewed publications.[17,18,20,26,31,43,46–99] An additional 7,654 mesh removals are reported in patient series investigating sling complications.[6,9,10,41,44,100–114] Use of imperfect research methodologies, a lack of long-term follow up and reporting bias have been suggested as causes of these differences.[10,45,115,116]

Safety and risk:benefit considerations

Safety of SMUS surgery refers to the probability of any adverse event, while risk describes the range and probability of specific adverse events. Demonstrating risk is relatively easy, but assessing safety is much more difficult. Any known adverse event is a risk, regardless of how infrequently the event has been reported or observed. Even a single case report of an adverse event establishes the existence of a specific risk, although without knowing the denominator, accurate assessments of the safety of sling surgery are impossible. The problem, simply stated, is that no well-controlled long-term safety studies with published results currently exist, nor do any good registries in this area. In lieu of this lack of conclusive evidence, we present current data, which, at its best, represent the minimum risks associated with SMUS implantation and long-term use (Tables 1 and 2). Major risks of SMUS surgery, which should be weighed up by patients considering undergoing these procedures, include those requiring further surgery and those that are refractory to treatment. Complications that lead to further surgery include urethral obstruction (3.2%), vaginal, bladder and/or urethral erosion (2%) and fistulas (0.3%). In addition, we estimate that bowel perforation and serious infections have a combined incidence of about 0.1%.[117–134] Refractory and potentially lifestyle-altering complications include chronic pain (4.1%) and *de novo* overactive bladder (OAB) in 11% (Table 5), although the number of patients with *de novo* OAB who are refractory to treatment remains unknown. Evidence suggests that well over 50% of patients with OAB of any aetiology discontinue medical treatment within 1 year, owing to a combination of poor effectiveness and low tolerability.[135–137] For the purposes of this discussion we made a conservative estimate that 35% of patients with *de novo* OAB following SMUS surgery are refractory to treatment, which suggests that approximately 3.9% of patients who have undergone SMUS surgery will have refractory OAB (Box 1).

Establishing safety, defined as the chances of having an unsatisfactory outcome following sling surgery, is an important step in enabling accurate patient decision making. Many patients with both chronic pain and *de novo* OAB have previously undergone SMUS revision surgery; however, simply adding together the complication incidences to give an accurate indication of safety is impossible, as the available data are not sufficiently reliable to produce an accurate estimate this way. For the purposes of this discussion, we have made our best estimate of the safety of SMUS surgery utilizing the data summarized in the preceding paragraph.

The reported 5-year failure rate of SMUS surgery in patients with SUI ranges from 5% to 26% (Table 1),[16–23,26,27,29] and the reported incidence of *de novo* SUI after sling excision surgery ranges from 10–62%.[9,43,78,84,85,94,100,138] From these data, we estimate the lowest rate of recurrent and/or persistent SUI among patients who underwent SMUS surgery to be 5.3%. Furthermore, we conclude that the lowest estimated risk of serious complications of SMUS surgery is 13.6% and the additional risk of failure with respect to the original procedure (with respect to SUI) is 5.3%. These estimated data reflect the minimum risks reported in the literature, the actual risks could be considerably higher.

The ability of both physicians and patients to make informed decisions regarding sling surgery is predicated on an accurate understanding of the risk:benefit ratio. The benefits of sling surgery, with respect to effectiveness, have been well documented. By contrast, the risks associated with SMUS surgery are poorly understood

Table 4 | Complications of patients with a TOT sling

Complication	*n*	Complications (% of patients)	Incidence (mean; range)
General complications			
Death within 30 days*	4,044	0 (0.0)	0.0
Urethral obstruction/voiding dysfunction	8,287	406 (4.9)	5.9; 0–33.9
Requiring surgery	5,001	75 (1.5)	2.0; 0–21.3
Urinary infections	4,003	226 (5.6)	6.2; 0–23.3
Pain (within 6 weeks)	2,964	262 (8.8)	10.2; 0–33.3
Neurologic symptoms (within 6 weeks)	1,249	28 (2.2)	0.9; 0–10.3
De novo OAB	6,215	519 (8.4)	10.3; 0–48.1
Pelvic organ perforation			
In total	5,856	143 (2.4)	2.3; 0–16.1
Bladder	4,872	60 (1.2)	1.1; 0–16.1
Vaginal	4,582	80 (1.7)	1.6; 0–14.1
Urethral	4,296	2 (0.0)	0.0; 0–0.3
Bowel	3,020	0 (0.0)	0.0
Ureteral	3,020	1 (0.0)	0.0; 0–1.3
Mesh exposure/erosion/extrusion			
In total	8,293	196 (2.4)	2.7; 0–19.0
Treated conservatively	7,648	64 (0.8)	1.0; 0–7.1
Vaginal	6,739	52 (0.8)	1.0; 0–7.1
Bladder	6,739	0 (0.0)	0.0
Urethral	6,739	0 (0.0)	0.0
Requiring surgery	7,901	132 (1.7)	1.9; 0–15.9
Vaginal	6,528	98 (1.5)	1.8; 0–15.9
Bladder	6,528	3 (0.0)*	0.0
Urethral	6,528	7 (0.1)	0.0; 0–2.6
Longer-term complications			
Refractory pain (>6 weeks)	4,756	204 (4.3)	5.3; 0–30.5
Neurologic symptoms (>6 weeks)	1,541	32 (2.1)	0.9; 0–10.6
Fistulas	322	1 (0.3)	0.2; 0–1.1

*Case series only investigating bladder erosions were removed from the analysis. Abbreviations: OAB, overactive bladder; TOT, transobturator tape.

and poorly documented. Some risk factors, such as prior pelvic radiation or surgery, concomitant urethral diverticular surgery, the surgical learning curve and an individual surgeon's skill set are accepted risk factors, yet even these risk factors are not well documented in peer-reviewed publications. Thus, accurately prognosticating the risks of SMUS surgery for any particular patient is difficult.

Owing to the limitations inherent in the evaluation of risk and safety described in this section, we can estimate that, based on the available literature reports, a minimum of 12.5% of women who undergo mesh SMUS surgery have a serious adverse event and/or surgical failure, although limited data are available on prognostic indicators.

Perioperative complications

Methods used to identify and classify perioperative complications vary widely between studies. A classification system originally devised in 2004 based on severity of complications[139] was modified for use by the Urinary Incontinence Treatment Network, a multicentre collaboration supported by the National Institute of Diabetes and Digestive and Kidney Diseases, a branch of the NIH.[30,39,140,141] Investigators in this network defined minor complications (or minor adverse events) as those not requiring surgical intervention that were treated expectantly or with medication (grade 1–2). Major complications (serious adverse events) include those requiring one or more surgical procedures, and life-threatening complications are defined as those requiring management in an intensive care unit and often resulting in patient death (grade 3–5).[30] Bladder or urethral trocar perforation was considered to be a serious adverse event whether or not further intervention was necessary. Another classification scheme, the Accordion system,[120] enables postoperative complications to be categorized into in four levels of severity: mild, moderate, severe, and death.[44,142]

However, sorting complications into groups based solely on the severity of their presentation and treatment might be misleading in the absence of adequate follow-up monitoring. For example, patients with apparently minor complications such as vaginal exposure that is initially treated with local excision and primary closure might present with dyspareunia or recurrent exposure long after the follow-up period has expired.[9,31,41–44] Indeed, many patients in one of our own studies presented in exactly this way, but this fact was never captured in the paper owing to the methodology used.[9] We have seen many unreported examples of patients managed conservatively with short-term success, who ultimately presented with a recurrent complication that occurred after the study ended, owing to the short follow-up duration of most published research (1–2 years) relative to the expected lifespan of most implanted slings.[9,81,105,143–147] Authors of one study estimated the overall incidence of vaginal extrusion of mesh and pelvic pain to be 6% and 4.3%, respectively.[45] Despite peer-reviewed literature in this area being replete with statements about the short-lived nature of sling-related complications, most case reports of mesh sling complications document the treatment-refractory nature and suboptimal outcomes associated with these complications, none of which was captured by the original studies.[9,43] For some complications (cystitis, voiding dysfunction, pain or neurological symptoms), most authors claim that only expectant or medical treatment is necessary and that patient outcomes are satisfactory, without presenting any meaningful follow-up data to substantiate these claims.[30,146,148,149]

In 2011, the International Urogynaecology Association (IUGA) and the International Continence Society (ICS) published a joint recommendation for a standardization of terminology to report complications related to the insertion of prostheses and grafts in female pelvic floor surgery.[150] To date, these guidelines have not been widely used. The net result of all of this is that the science of assessing and reporting midurethral sling complications is seriously flawed.

Table 5 | Comparison of complications of patients with an RP sling or TOT sling

Complication	RP sling (mean; range)	TOT sling (mean; range)	Combined RP and TOT sling (mean; range)
General complications			
Death within 30 days	0.0	0.0	0.0
Urethral obstruction/voiding dysfunction	8.8; 0–32.7	5.9; 0–33.9	7.3; 0–33.9
Requiring surgery	2.7; 0–8.9	2.0; 0–21.3	2.3; 0–21.3
Urinary infections	8.6; 0–39.1	6.2; 0–23.3	7.3; 0–39.1
Pain (within 6 weeks)	4.5; 0–23.1	10.2; 0–33.3	7.9; 0–33.3
Neurologic symptoms (within 6 weeks)	1.6; 0–5.0	0.9; 0–10.3	1.2; 0–10.3
De novo OAB	11.4; 0–29.4	10.3; 0–48.1	10.9; 0–48.1
Pelvic organ perforation			
In total	4.8; 0–14.3	2.3; 0–16.1	3.5; 0–16.1
Bladder	4.6; 0–14.3	1.1; 0–16.1	2.9; 0–16.1
Vaginal	1.0; 0–2.1	1.6; 0–14.1	1.4; 0–14.1
Urethral	0.0; 0–1.5	0.0; 0–0.3	0.0; 0–1.5
Bowel	0.0; 0–1.7	0.0	0.0; 0–1.7
Ureteral	0.0	0.0; 0–1.3	0.0; 0–1.3
Mesh exposure/erosion/extrusion			
In total	2.3; 0–26.1	2.7; 0–19.0	2.5; 0–26.1
Treated conservatively	0.1; 0–5.6	1.0; 0–7.1	0.9; 0–7.1
Vaginal	0.0; 0–4.6	1.0; 0–7.1	0.7; 0–7.1
Bladder	0.0; 0–5.6	0.0	0.0; 0–5.6
Urethral	0.0	0.0	0.0
Requiring surgery	1.6; 0–26.1	1.9; 0–15.9	1.8; 0–26.1
Vaginal	1.0; 0–10.9	1.8; 0–15.9	1.5; 0–15.9
Bladder	1.4; 0–15.2	0.0*	0.2; 0–15.2
Urethral	0.3; 0–16.7	0.0; 0–2.6	0.2; 0–16.7
Longer-term complications			
Refractory pain (>6 weeks)	2.0; 0–7.9	5.3; 0–30.5	4.1; 0–30.5
Neurological symptoms (>6 weeks)	1.0; 0–5.2	0.9; 0–10.6	1.0; 0–10.6
Fistulas	0.4; 0–0.7	0.2; 0–1.1	0.3; 0–1.1

*Case series only investigating bladder erosions were removed from the analysis. Abbreviations: OAB, overactive bladder; RP, retropubic tension-free transvaginal mesh tape; TOT, transobturator tape.

Infection

In a randomized study of SMUS effectiveness, investigators found culture-proven cystitis in 8.4% of patients with RP and 4.7% with TOT slings.[30] In another study, the authors reported that 12% of patients developed at least one UTI in the first 3 months after RP sling surgery.[151] Our literature search documented bacterial cystitis in 0–39% of patients who underwent SMUS surgery (REFS 13,18,21–23,30,39,47,48,50,53,55–57, 59,61,66,74,76,83,91,152–186). Unfortunately, limited published data are available on the long-term consequences of these infections. For example, in one study, 7.3% of women had recurrent UTIs 12 months after being fitted with a TOT sling, but no published reports of longer-term follow-up currently exist.[76]

Other more serious infections have been reported after SMUS implantation. In a comprehensive literature review[45] several such complications following sling placement were reported: cellulitis;[117–121,187] abscess formation, including in the retropubic space,[122] retroperitoneal space,[123] thigh,[123] obturator space[124–126] and ischiorectal fossa;[127,128] sinus tract formation;[129] necrotizing fasciitis;[130] osteitis pubis;[131] and sepsis.[12] Thigh abscesses, a complication unique to the TOT sling approach, have been reported in the past decade.[101,123,188,189] Occurrence of such serious SMUS-related infectious complications is often delayed by months or years after sling implantation. Presenting symptoms include chronic discharge from the vagina, thigh and/or perineum.

Treatment of infected mesh and abscesses requires open drainage and removal of all mesh, which, otherwise, will serve as a nidus for further infection. Amid types II and III mesh materials,[190] such as Silastic® (Dow Corning, MI, USA) and Gore-Tex® (W.L. Gore & Associates, DE, USA), are easily identified and pulled out, usually in their intact form. The technical challenges of removing type I meshes are considerably greater. For example, even though the entire mesh is likely to be infected, only part of it is involved in the abscess. This part is easy to remove, but because of tissue ingrowth and probable degradation, the remaining mesh is usually embedded in the tissue and might fragment during dissection. Furthermore, the retropubic and thigh portions of RP and TOT slings, respectively, are notoriously difficult to remove.[9,43,78,84,85,94,100,138] RP slings are often adherent to the bladder neck and difficult to access during surgery. We, and others, have noted that the infection can track along muscle planes and even form a psoas muscle abscess in some patients.[123,191] These abscesses might require multiple operations in order to achieve a satisfactory outcome. Unfortunately, owing to the technical reasons explained above and concerns about complications in adjacent organs during the dissection, complete mesh removal is often not accomplished in patients with type I mesh slings. Necrotizing fasciitis (Fournier gangrene) has also been reported after both RP[192] and TOT[193] sling implantations. In patients with SMUS-related infections, removal of the complete mesh is particularly important. Of course, many more serious infectious complications are likely to arise from the 'minor' ones listed above,[113,126] but we could find no published studies that actually address this issue.

Pelvic organ perforations

Pelvic organ (bladder, urethral, vaginal [REFS 10,14, 16,18,21–23,30,33,39,47,48,50,52,53,55,56,59,62–64, 66,67,69–71,73,74,76,77,80,81,86–88,90–93,98, 99,109,132–134,140,145,146,148,151–153,156,158, 162,163,167,168,171,173,176–179,181–184,194–238], or bowel) perforation at the time of trocar passage has been reported to occur in 0–16% of sling surgery procedures (0–14% for RP sling implantation and 0–16% for TOT sling implantation). In most reports, the authors usually downplay any substantial implications of pelvic organ perforations. Authors will typically state that

Box 1 | Summary of mesh safety

Complications requiring surgery

- Urethral obstruction 3.2%
- Erosion, extrusion or exposure 2.0%
- Fistulas 0.3%
- Bowel injury or infection 0.1%
- Lifestyle-altering complications
- Chronic pain 4.3% (0.5%)*
- Refractory (*de novo*) OAB 11% (3.9%)*
- Recurrent and/or persistent SUI 5.3%
- Total incidence of serious complications and/or sling failure in patients with incontinence 15.3%

*Indicates numbers are not mutually exclusive to individual complications. For example, a patient who underwent mesh excision for exposure may develop refractory pain. The numbers in parenthesis refer to the estimated incidence of complications refractory to medical or surgical treament. Abbreviations: OAB, overactive bladder; SUI, stress urinary incontinence.

recognized trocar perforations of the bladder might be treated by simply removing the trocar (or sling) and passing it again and, at the discretion of the surgeon, leaving an indwelling catheter in for a matter of days or, sometimes, not at all.[148,239–242] However, in an article published in 2014, the authors concluded that occurrence of bladder and/or urethral perforations during surgery is associated with an almost 26-fold increase in risk of subsequent bladder or urethral mesh erosion.[31] If the findings of this study are accurate, the dictum of simply removing and repassing the trocar after bladder perforation must be seriously questioned.

Limited information is available on urethral complications following perforation, but if a perforation large enough to necessitate repair exists, most would agree that it is best to abandon the SMUS procedure.[39,62,64,73,140,213] Depending on the circumstances, buttressing the repair with a Martius flap in anticipation of performing an autologous or allograft sling procedure at another date is one possible approach; alternatively, in rare circumstances, when it is desirable to complete the surgery in one sitting, this could be done at the same time as sling implantation.[9,43,243] Such a situation might arise when a patient's health dictates that the risk:benefit ratio favours a single operation instead of two or, if the patient lives at a great distance from the treatment centre and returning for a second operation would present a major burden.

Bowel perforations during sling surgery are even more uncommon than perforations of other pelvic organs with a reported incidence in 0.005–0.02% of procedures.[132] In a meta-analysis published in 2007, authors reported a mortality rate of 20% in 35 incidences of bowel perforation during sling surgery.[133] Of particular concern is the fact that some patients did not present with any clinical signs of abdominal injury.[102,104,106,132–134,236] Patients' initial complaints were often originally attributed to voiding dysfunction and not until days later, when the patients became seriously ill, was the correct diagnosis made.[237] In five patients the diagnosis of bowel perforation during sling surgery was made only at autopsy.[238]

Voiding dysfunction

The term 'voiding dysfunction' was not clearly defined in the majority of studies in this area and could be interpreted as either voiding symptoms, storage symptoms or both. Some of the terms used include *de novo* or persistent overactive bladder, urgency or urge incontinence, urinary retention and urethral obstruction from SMUS. In addition, secondary voiding problems can arise after sling revision or excision surgeries performed to treat the original complications such as recurrent SUI, dyspareunia, urethral strictures and fistulas.[41,100,111,244] We used our best judgement to assign the authors' intent to one of the categories listed below, but in some instances the author's intent was not clear. For example, one category was listed as "voiding dysfunction requiring surgery",[30] although whether this was a result of urethral obstruction or refractory OAB was not defined. Keeping in mind the caveats listed above, temporary or refractory voiding dysfunction has been reported in 0–33% of patients with a SMUS, and is more common in patients fitted with an RP sling than in those fitted with a TOT sling (REFS 16–23,26,30,33,39,46,47,49–51, 53,54,56,58,59,61–66,68–71,73,74,76,77,79,80,82, 83,86–93,95,97–99,140,145,146,148,151–153,156–164, 166–171,173,174,176–184,186,194–205,207,208, 211,214–218,220,222–229,231–233,235,245–260).

OAB symptoms

The terms used to describe OAB in the studies reviewed included urge or urgency incontinence, urgency, refractory urgency and overactive bladder.[9,261] In addition, the qualifiers persistent or *de novo*[261] were often used. *De novo* OAB, indicating the occurrence of OAB after sling surgery, was reported in 0–48% of patients in various studies (REFS 17,18,20,26,39,46–48,50–53, 55,57–59,61,62,66,67,70,73–77,79,83,87,88,91,92, 96,97,99,140,152,153,155,157,159,161,163,164,166–168, 170–174,177,178,181–186,209,211,213,216–219,222, 224,228,229,231–235,245,249,254,255,259,262–269). Most patients with OAB had symptoms that were said to have resolved within the first month of surgery either spontaneously, or in response to anticholinergics, antibiotics or self-catheterization.[30,194] However, the metrics used to conclude this were inadequate for the task; in fact, the vast majority of studies used no metrics or validated outcome measures at all. When validated instruments were used, they were often, in our judgement, inadequate. For example, the UDI was one of the most common questionnaires used and, as alluded to above, conflates the degree of incontinence with bother.[24] Furthermore, the UDI contains no question that specifically refers to urgency (as opposed to urge incontinence). Approximately two-thirds of women with OAB do not have urge incontinence;[270] thus, use of this instrument is likely to miss two-thirds of the women with urgency or OAB in any series.

In patients with refractory OAB as a SMUS-related complication, a careful search for a remediable underlying aetiology should be conducted. Possible aetiologies include infection, stones, urethral obstruction

and mesh erosion into the bladder or urethra. When such aetiologies are found and treated, the reported success rates are generally high, but the methods used to determine treatment success were generally of poor quality. For example, in reports from two studies of endoscopic laser ablation of eroded mesh in patients with OAB the authors reported successful outcomes, but did not use any objective outcome measures.[100,108] Other studies did use validated instruments to quantify outcomes such as the Overactive Bladder Symptom Score, voiding diaries and pad-weight tests.[9] With these caveats in mind, a successful outcome after surgical treatment of these remediable conditions was reported in 28–64% of patients with refractory OAB as a SMUS-related complication.[9,30,43,85]

Urethral obstruction

Urethral obstruction is a urodynamic diagnosis based on high detrusor pressure accompanied by low urine flow rate, although again, no uniform criteria for diagnosing obstruction were used in the papers reviewed. Most investigators simply inferred obstruction based on the temporal relationship between SMUS surgery and voiding symptoms.[271,272] Others used measurements of urine flow rate and post-void residual volume or urodynamics. Urethral obstruction should be suspected in any woman with persistent voiding symptoms (either storage or emptying) after SMUS placement.[9,94,273,274] Obstruction is definitively diagnosed by the findings of high detrusor pressure and low uroflow during urodynamics. Generally, the existence of a normal urine flow rate is thought to exclude the presence of urethral obstruction; however, this is not always the case, as sometimes abnormal urine flow rate can be generated by a strong detrusor contraction or abdominal straining (Figure 1).

Even in the absence of urodynamically confirmed urethral obstruction, sling incision and/or excision can completely resolve refractory voiding (and OAB) symptoms. Compression from the sling is by far the most common cause of urethral obstruction, and at least one case of urethral stricture accompanied by urethral erosion has been reported.[9] The incidence of urethral obstruction requiring surgical intervention ranges from 0% to 8.9% in patients fitted with RP slings and from 0% to 21.3% for those with TOT slings (REFS 17,18,20,21,23,26,30,46–48, 50–56,58,59,61–64,66–69,71,74,77,80–83,86–92,97–99, 148,159,163,166,173,178,180–182,216–218,233,245,250, 253,255,258–260,269). In the largest patient series reported to date, which comprised nearly 190,000 SMUS implantation procedures, and was based on insurance data, a 9-year cumulative rate of sling revision surgery owing to urethral obstruction of 1.3% was reported. Most of this revision surgery occurred in the first few years after the original implantation procedure.[6] In this patient series, however, no mention of the number of patients lost to follow-up monitoring was made, and because investigators only searched for one Current Procedural Terminology (CPT) code (57287) for the sling revision surgery, the actual incidence of revision surgery owing to urethral obstruction was possibly higher. Similarly, a rate of urethrolysis of 3.4% was reported in a cohort of 818 patients fitted with RP slings, although investigators failed to search for 'mesh removal', 'explant' or 'excision'.[275] Owing to incomplete use of these search terms, retrospective studies of databases[6,270] are prone to underestimating the incidence of urethral obstruction requiring surgery.

The reported incidences of urethral obstruction requiring surgery are generally well under 10%. A small number of patients having urethral obstruction in the lost-to-follow-up group could substantially increase the actual overall incidence. In fact, most studies found that 50–75% (sometimes more) of patients undergoing sling revision surgery were treated by a surgeon other than the implanting surgeon.[9,44,276]

Some authors have recommended sling incision or even urethral dilatation for treatment of patients with urethral obstruction, although most authors agree that the entire suburethral portion of the sling should be removed, even if an incision into the wall or urethral lumen is required.[9,40,154,244,261] Whether to remove all of the mesh from RP slings in patients with urethral obstruction depends on multiple factors, including associated pelvic pain, dyspareunia and/or recurrent infections that might be related to retained mesh.[277–280] No meaningful data exist regarding the effectiveness of urethral dilatation; however, based on our clinical experience, we believe that this approach should not be used owing to the possibility of a urethral abrasion that might ultimately lead to erosion.[281] Of course, optical urethrotomy, internal urethrotomy and transurethral incision of urethral strictures should not be done at all except in the rarest of circumstances, for fear of causing iatrogenic urethral exposure.

No clear indications for urethrolysis currently exist; rather, the need for procedures of this type should be considered on a patient-by-patient basis, depending on the degree of scarring and urethral immobility.[282,283] In our judgement, urethrolysis should be considered in patients in whom the proximal urethra feels scarred and immobile during surgery and/or following a finding of limited urethral mobility on a Q-Tip® (Unilever, London, UK) test.

A high, and well documented incidence of recurrent SUI after mesh revision surgery exists, that is reported to range from 10% to 60% of patients who undergo revision surgery.[9,43,78,84,85,94,100,138] For each patient with symptoms of recurrent sphincteric incontinence, a decision needs to be made as to whether or not another anti-incontinence procedure should be considered. Reports of sling revision surgery in patients with sphincteric incontinence are sparse, and often anecdotal; but, if urethral reconstruction is necessary at the time of mesh removal, the AUA guidelines on the surgical management of female SUI[1] state that implantation of another SMUS are contraindicated in these patients. Most authors recommend a wait-and-see approach to management of patients with recurrent SUI after mesh revision surgery, and, as a rule, we agree with this

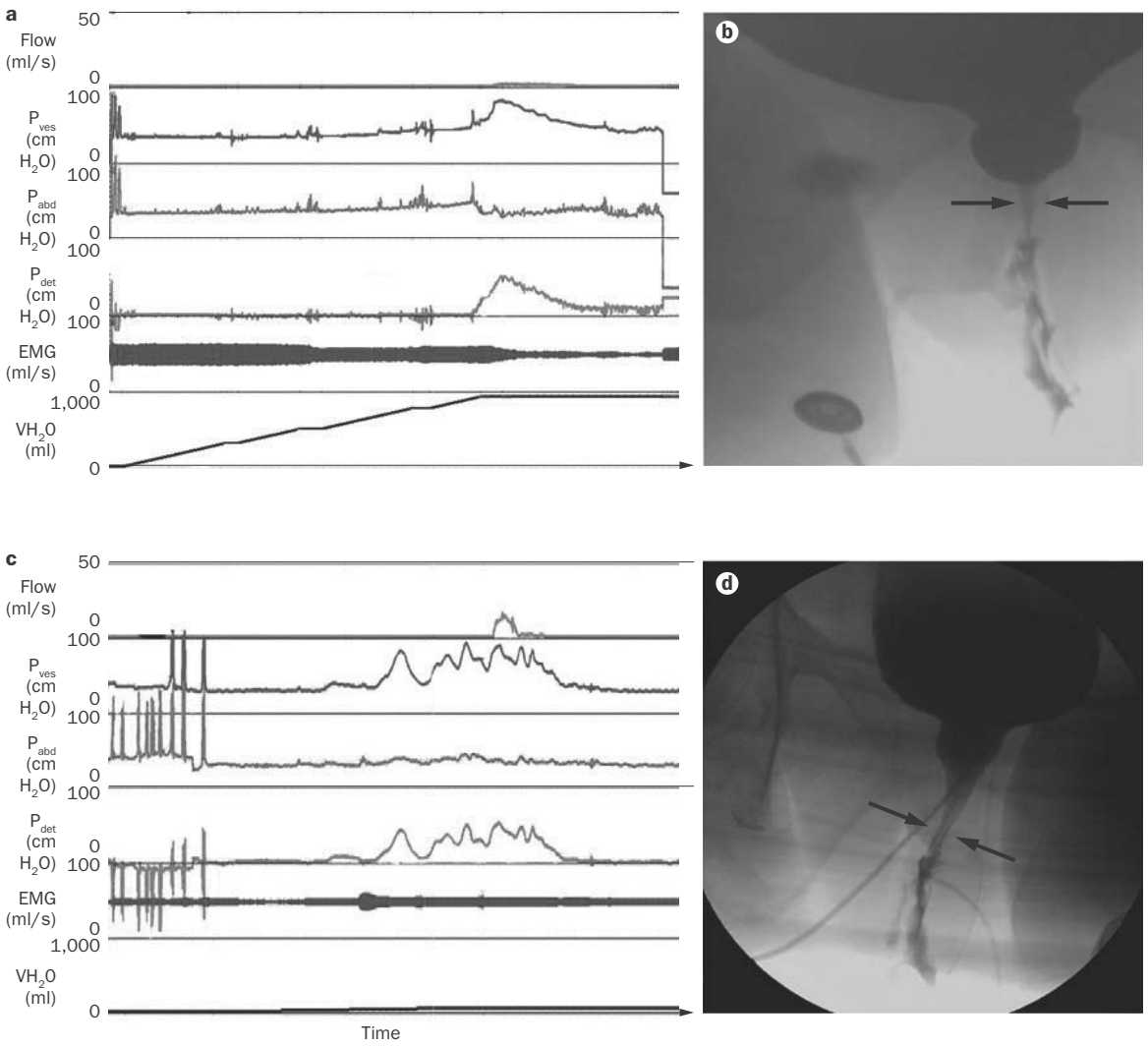


Figure 1 | Identification of urethral obstruction. **a** | Urodynamic trace showing severe urethral obstruction (Blaivas–Groutz nomogram type 2) caused by the presence of a urethral stricture in a 52 year-old woman 4 years postimplantation of a SPARC™ (American Medical Systems, MN, USA) SMUS. Urethral obstruction is confirmed by the presence of strong, sustained detrusor contraction ($P_{det}Q_{max}$ = 56 cm H_2O and Q_{max} = 1 mL/s). **b** | Cystourethrogram confirming the presence of an obstruction owing to the presence of a midurethral stricture (arrows). **c** | Urodynamic trace showing high-flow urethral obstruction in a 52 year-old woman 6 years after midurethral SMUS implantation. Urethral obstruction was confirmed by $P_{det}Q_{max}$ = 56 cm H_2O (Blaivas–Groutz nomogram type 1). Owing to a technical error, infused volume was not recorded on this trace. **d** | Voiding cystourethrogram showing the site of urethral obstruction to be in the distal third of the urethra (arrows). Abbreviations: EMG, electromyogram; P_{abd}, abdominal pressure; P_{det}, detrusor pressure; $P_{det}Q_{max}$, voiding pressure at peak flow; P_{ves}, intravesical pressure; Q_{max}, peak flow; SMUS, synthetic midurethral sling; VH_2O, bladder filling volume.

recommendation. However, data from two published reports contradict this recommendation. A continence rate of 71% was reported in 14 patients who underwent mesh removal after urethral perforations and, in another study, an 82% success rate after revision surgery was reported in 28 patients, of whom 14 had a synchronous autologous sling. In both series a Martius flap was placed between the urethra and sling.[9,43,243] No clear indications exist for conducting synchronous anti-incontinence surgical procedures during mesh excision surgery, although we believe that this approach should be considered whenever extensive damage to the proximal half of the urethra has occurred. Authors of most study reports, however, do not report thoroughly on the outcomes of sling excision surgery.

Mesh erosion, extrusion or exposure

Reports of research in this area of sling complications are typically replete with terminology that conflates the terms erosion, extrusion and exposure; thus, discerning the exact meaning of every author was often impossible. The joint recommendations of the IUGA and ICS[150] provide guidance regarding use of terminology related to SMUS complications, but, in a clinical sense, applying the recommended distinctions is usually not possible in most patients. The IUGA and ICS guidelines define exposure as "a condition of displaying (mesh), revealing, exhibiting, or making accessible for example through the vagina"[150] and extrusion of mesh as "passage gradually out of a body structure or tissue".[150] The guidelines also recommend avoiding use of the term 'erosion' altogether,

but in this Review, we use the terms interchangeably as there is no sound scientific way of making this distinction exists given that the overwhelming majority of authors use this terminology interchangeably. Conceptually, mesh can be seen to protrude through the vaginal wall or into the bladder, urethra or bowel by one of two mechanisms: either it was inadvertently positioned there at the time of surgery or somehow, over the course of time, the mesh gradually worked itself into such a position.

The incidence of mesh sling erosions varies widely between study reports, ranging from 0% to 41% of patients (REFS 16–20,22,26,30,31,39,46–50,52,53, 55–73,75–77,79,81,82,86–90,92,93,95–100,152,153, 155–160,162,164,166–179,181–185,204,207–209, 212–215,217–221,224,225,229,231,233–235,245,247, 252–255,257–259,265,266,268,284–293). The risk factors for sling erosion fall into three main categories: patient factors; mesh characteristics; and intraoperative considerations.[42] With respect to the patient, oestrogen-deficient states, genital atrophy, surgical scarring, concurrent prolapse surgery, type 1 or type 2 diabetes mellitus, steroid use, concurrent anticholinergic use and smoking have been reported as risk factors for sling erosion.[246] Patients ≥75 years of age also had a higher incidence of OAB and recurrent UTI[266] and patients of both younger and older ages (mean ages 55, and 75 years respectively) were variously reported as having adjusted risk factors. Previous pelvic radiation is another obvious risk factor for mesh erosion, but few of these patients undergo sling surgery; thus, this factor did not appear as such in the literature.

Certain types of mesh have a particularly high risk of erosion based on the intrinsic characteristics of the materials they are made from. In a study published in 1997,[190] synthetic materials used for herniorraphy (a type of hernia repair surgery) were categorized based on their composition (synthetic or biological), structure (monofilament or multifilament), pore size (macroporous or microporous) and architecture (knitted or woven). Type I (knitted, monofilament and macroporous polypropylene mesh) is currently considered to be the optimal SMUS mesh material owing to its large pore size (>75 μm), which facilitates infiltration of macrophages and fibroblasts, promotes neovascularity and tissue ingrowth, and minimizes the likelihood of infection. Examples of Type I mesh include VitaMESH™ (Atrium, NH, USA), Marlex® (C.R. Bard, NJ, USA), Prolene® (Ethicon, NJ, USA) and Trelex Natural® mesh (Boston Scientific, MA, USA).

In an attempt to decrease the foreign body responses associated with mesh materials and increase tissue compliance, several manufacturers have designed lightweight meshes of decreased density with smaller fibre diameter and larger pores, with the intention of preventing stiffness, contraction and mesh shrinkage. Several published studies purport some benefit of these new materials in patients requiring inguinal hernia repair; however, all of the studies involved small numbers of patients, with limited follow-up duration, thus precluding any meaningful conclusions.[35,294–300]

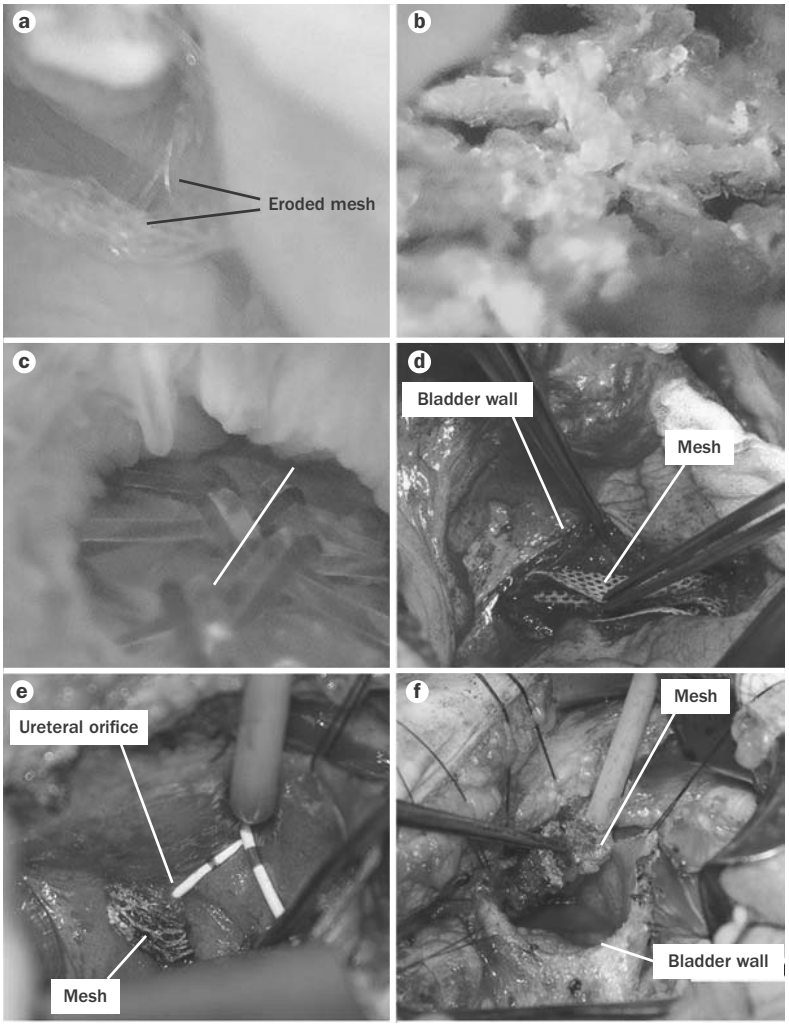
Amid type II mesh (monofilament and microporous) has pores (<10 μm in diameter) that are large enough to allow bacterial infiltration but too small for macrophage infiltration, thus infection is more probable and tissue ingrowth is impeded.[190] Polytetraflouethylene (PTFE, Gore-Tex® W.L. Gore & Associates, DE, USA) is the most common prototype type II mesh. Surgical Membrane Type III multifilament mesh is much denser and stiffer than other types of mesh and has interstices that are <10 μm in diameter with the same negative consequences as those of type II mesh. PTFE mesh (Teflon® DuPont, DE, USA), braided polyethylene terephthalate mesh (Mersilene® Ethicon, NJ, USA), braided polypropylene mesh (Surgipro™ [Covidien, CA, USA] monofilament mesh) and perforated PTFE patch (GORE® MYCROMESH® W.L. Gore & Associates, DE, USA) are examples of type III meshes. Type IV meshes are submicroporous coated biomaterials with pores <1 μm in diameter. SILASTIC® (Dow Corning, MI, USA), Celgard® polypropylene sheeting (Celgard, NC, USA) GORE® PRECLUDE® Pericardial membrane and GORE® PRECLUDE® Dura-substitute (both manufactured by W.L. Gore & Associates, DE, USA) are all type IV meshes. Types II–IV meshes, including PTFE mesh (Amid Type II), silicon-coated polyethylene or polyester (Amid Type IV) and non-knitted, nonwoven mesh such as OBTAPE® and UraTape® (both Mentor–Porges, Le Plessis Robinson, France), have been documented to have a much higher incidence of erosion (16–25%) compared with that of type I meshes (0–10%).[105,109,124,301]

As described previously, bladder, urethral or vaginal perforation during the original surgery increases the risk of subsequent sling erosion by approximately 26-fold.[31] In addition, passage of the trocar through the vaginal, bladder or urethral wall without actually penetrating the lumen might occur, which would result in positioning of the mesh just barely under the surface of the lumen and predisposing it to erosion. This possibility seems likely, although it is currently unproven.

The approach to treatment of sling erosions has been largely empirical, follow-up durations of studies in this area have been short and only a few studies have applied validated outcome measures, especially with respect to the occurrence of other symptoms, such as lower urinary tract symptoms, pain and dyspareunia.[9,44] As discussed previously, recurrent SUI after mesh removal is not uncommon.[9,43,78,84,85,94,100,138] However, synchronous anti-incontinence surgery can be effective in this setting.[43] The authors of this study[40] based their decision to conduct synchronous autologous sling surgery on multiple factors: the location of the urethral injury; preoperative continence status; and the degree of urethral hypermobility. In our series,[9] the success rate (based on PGII score) was 82% after mesh removal, but only half of the patients underwent synchronous autologous sling surgery.[9]

Mesh erosion in the bladder

Bladder erosions are reported to occur in 0–15% of patients fitted with a SMUS (REFS 16–20,22,26,30,46–48,



◀ **Figure 2** | Identification and removal of eroded mesh. **a** | Eroded mesh can be difficult to see during cystoscopy owing to its almost translucent appearance in some patients. **b** | In this erosion, the sling is nearly obscured by the presence of calcium deposits. **c** | Appearance of eroded Amid Type I mesh at urethroscopy. This mesh had no appreciable tissue ingrowth and pulled out of the urethra easily, leaving a small urethrotomy that was closed with a few sutures. **d** | Surgical explantation of eroded silicone mesh. In this case, removing the mesh was relatively easy because it was an Amid type IV mesh, which was encapsulated. **e** | Transvesical explantation of an eroded mesh sling. This type I mesh had tissue ingrowth and required delicate surgery and sharp dissection to enable removal. **f** | Following sharp dissection, the mesh was completely excised from the bladder wall. It coursed over, but did not damage, the ureter. Permission obtained from Fred Govier and Kathleen Kobashi, Virginia Mason Hospital & Seattle Medical Center, Seattle, WA, USA.

50,52,53,55–73,75–77, 79,81,82,86–90,92,93,95–100, 140,152,155–160,164,166–168,170–172,174–177,181, 183–185,207–209,213,215,217–219,221,229,231,233, 234,245,247,253,254,257,258,260,265,266,288–293). Patients with mesh erosions in the bladder usually present with recurrent UTIs, haematuria, bladder stones, incontinence, dyspareunia and pelvic pain; mesh erosions are typically discovered during cystoscopic examinations (Figure 2). Most authors agree on the general treatment principle—all mesh must be removed from the bladder—but the procedures used to do so vary widely. A variety of endoscopic approaches have been used to remove mesh including cutting with scissors and removing the mesh with grasping forceps, transurethral resection of the mesh using monopolar or bipolar current, vaporizing it with a holmium laser[302–310] and even utilizing a small nasal speculum or Metzenbaum scissors passed transurethrally alongside a cystoscope.[311] Results achieved with these surgeries[300–309] have been variable, with some successes followed up for as long as a few years, but the majority of studies had short follow-up durations. Open surgery using a suprapubic or vaginal approach has the advantage of removing all of the intravesical mesh, including mesh that traverses the bladder wall (Figure 2).[9,43,312] Sometimes, partial cystectomy is necessary to remove all the intravesical mesh;[9,10,313] laparoscopic approaches have also been tried.[138] Unfortunately, few studies of patients with mesh erosions in the bladder have sufficiently long follow-up durations or good enough outcome measures to determine the true success rates of these surgeries. Furthermore, all reported successes and failures were compared to the patient's status before the mesh removal surgery, and not before SMUS implantation surgery.

Mesh erosions in the urethra

Urethral erosions are much less common than bladder erosions in patients fitted with a SMUS, with a reported incidence of 0–2.6%.[46,61,100,176] Urethral strictures caused by mesh erosions are even rarer than urethral erosions.[314] A number of different aetiologies of urethral erosion have been postulated, including surgical transgressions (excessive sling tension, unrecognized urethral perforation and passage of the sling through the urethral wall), urethral dilatation,[281] postoperative contraction of the sling,[315] infection, inflammation and immunological reactions.[33,315–319] Treatment of urethral erosions might be as simple as excision of the mesh, which sometimes pulls easily out of the urethra, (Figure 2) or can involve extensive surgical excision of the mesh with part of the urethral wall requiring urethral reconstruction and a Martius flap (Figure 3).[320]

Vaginal mesh erosion, extrusion or exposure

Vaginal mesh erosion, extrusion or exposure has been reported in 0–19% of patients with a SMUS (0–11% of patients with an RP sling and 0–19% of patients with a TOT sling, REFS 16–20,22,26,30,31,46,48,50,53,58–60, 62,64,65,67,69,70,72,75–77,79,81,82,86–90,92, 95,97,103,140,156,158,160,164,167,170,175,177,183, 185,218,221,231,233,247,257,260,266,288,291,292). Factors associated with a higher incidence of mesh extrusion include trocar perforation of the vaginal wall during mesh implantation, previous pelvic surgery, diabetes, bleeding complications at the time of surgery, pelvic radiation, smoking, older age and vaginal incision length >2 cm.[31,42,321]

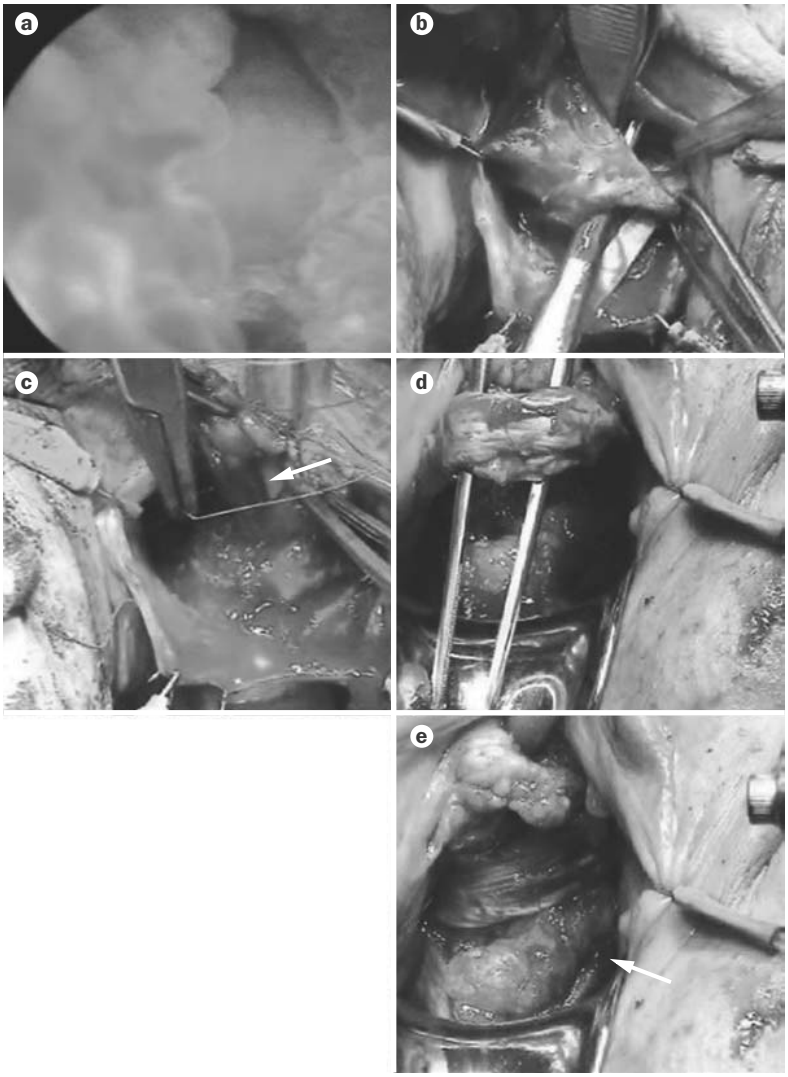


Figure 3 | Identification and removal of Amid type I eroded mesh surrounding the urethra. **a** | Urethroscopic view of urethral erosion. In this case the erosion was very subtle and located in the distal urethra, such erosions are very easy to miss. **b** | Transvaginal dissection and isolation of the mesh shown in image a reveals marked scarring and tissue ingrowth. **c** | Removal required sharp dissection that left a large defect in the urethra (arrow) that required urethral reconstruction, Martius flap and implantation of an autologous fascial sling. **d** | The sling being placed over the urethra. **e** | Creation of a Martius flap (arrow) between the reconstructed urethra and sling, thus repair is completed before vaginal wound closure.

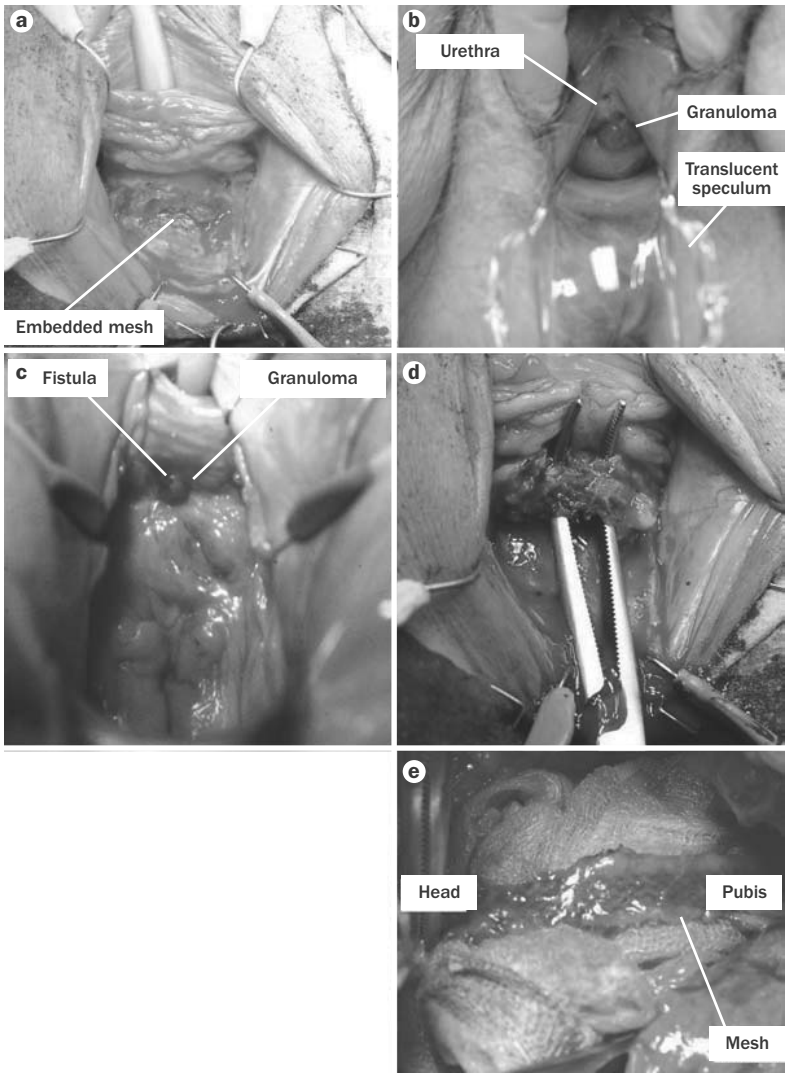
We postulate, based on our clinical experience, several other causes of vaginal mesh exposure including wound dehiscences resulting in exposure of the mesh or implantation of the mesh superficial to the pubocervical fascia so that it lies just beneath the surface.[9] When conditions that favour mesh erosions in the vagina are compounded by local ischaemia, inflammation, foreign body reaction and/or infection, the risk of erosion is likely to be increased. An alternative causative factor has also been suggested —defective wound healing caused by an immunological response to the mesh itself.[33] Vaginal mesh extrusion frequently presents as dyspareunia, vaginal discharge, vaginal bleeding and pain experienced by the sexual partner during vaginal intercourse ("hispareunia").[322] Sometimes asymptomatic extrusions are found during a routine vaginal examination. A diagnosis of vaginal mesh extrusion is typically based on a physical examination —by visual inspection and/or palpation (Figure 4). Most vaginal mesh extrusions occur within the first year of SMUS implantation, although they have been observed in patients as long as 17 years after the original surgery.[16] Some authors report that small areas of mesh exposure can be successfully treated with topical oestrogen,[323] although the results have been mixed.[324] Larger mesh exposures require primary closure of the vaginal wall over the exposed mesh or surgical excision and closure with or without vaginal wall flaps.[30,41–43,45] Mesh exposures of this type are usually reported as minor complications; post-treatment follow up in these patients has been woefully inadequate in most studies.[319,323–325] We did not find sufficient justification in the literature to be able to confidently assess the long-term success of treating these minor exposures. For example, in a retrospective review of nearly 347 complications, the authors found that 73% of patients who initially had nonsurgical treatment for vaginal mesh extrusions ultimately required surgical treatment within 5 years of the original sling surgery.[16,44] In a single-institution study of 79 patients who underwent SMUS implantation, the mean time from SMUS implantation to removal was 2 years with a range of 0–11 years. Despite the fact that mesh erosions can occur >10 years after implantation, most studies report a mean follow-up duration of only 2–23 months.[16,105,261,277,301,312,326]

Mesh erosions in the bowel

Bowel mesh erosions are exceedingly rare and all known patients with bowel erosions have presented with an enterovaginal fistula.[9,327,328] Treatment requires removal of all intra-abdominal mesh and repair or excision of the affected bowel. In our own clinical experience, a patient who had bowel mesh erosion had an associated vesicovaginal fistula and after several unsuccessful reconstructive surgeries required a continent urinary diversion.[9]

Pain

Pain is the most poorly studied complication of SMUS surgery; we found only a few studies that included prospective data collection and/or validated questionnaires assessing pain.[30,79,90,95,152,168,174,229,254] Some investigators used postoperative questionnaires that contained pain questions, but most relied on patients' recall or chart review.[39] In addition, many different descriptors of pain have been reported including vaginal, pelvic, groin, thigh, leg, suprapubic and lower abdominal pain, dyspareunia and "pain, patient self-report."[30] Two different kinds of pain caused by nerve injury have been suggested: centrally mediated hyperalgesia and a peripherally mediated painful hypoalgesia, suggesting the need for mechanism-based classification of neuropathic pain.[329] Most importantly, few of the case studies of patients with SMUS-related pain quantified the severity of this pain,



◀ **Figure 4** | Vaginal complications and removal of SMUS. **a** | View of mesh extrusion into the vagina. This extrusion was both readily visible and appeared palpable on physical examination. **b** | Transvaginal view of eroded mesh obscured by a granuloma. The erosion was neither visible nor palpable. **c** | Transvaginal view of fistula obscured by granuloma. **d** | Transvaginal explantation of an Amid type I RP sling. Note the dense tissue ingrowth and scar that requires sharp dissection in order remove the suburethral portion in its entirety. This portion of the sling felt thickened and stiff. **e** | Retropubic view in the same patient, as shown in image d. The retropubic portion of the mesh after dissection showed fatty tissue ingrowth. This portion was pliable and not scarred. Abbreviations: RP, retropubic; SMUS, synthetic mid-urethral sling.

its character or how the pain affected patients' quality of life.[30,64,82,263] This neglected topic is of the utmost importance and permanently affects "a small cohort of patients whose lives have been unalterably changed for the worse."[40,312]

Pain in patients with a SMUS has been attributed to direct nerve injury during implantation, nerve entrapment, haematoma, infection, chronic inflammation, structural changes to the implanted mesh (shrinkage, stiffening, hardening and/or banding) and scarring.[38,330] Most patients present with pain within the first year of surgery, although some present years later—as late as 8 years postoperatively.[9,110,143] In studies of effectiveness and safety, pain was mostly divided into perioperative pain and pain lasting more than 6 weeks. Perioperative pain has been reported in up to 33% of patients,[252] occurring more frequently after implantation of TOT slings than RP slings,[331] and chronic pain (of any definition) has been reported in 0–31% of patients (REFS 17,18,20,30,39,47,48,53,58,59,61–63,66,69,70,73,76,79,82,89–91,95,98,99,140,152,155,159,164,167,168,171–174,177,180–182,185,208,209,215,223,229,231–233,235,247,250,252,254,255,257,266,268,290,332,333).

Chronic disabling pain is one of the most common indications for mesh removal, particularly in patients fitted with TOT slings.[9,38,42,44,110,111,277,326] Chronic pelvic pain often contributes to a need for mesh removal; however, these data might not be captured by the approaches used by all investigators. Thus, the reported incidence of pain complications is likely to be falsely low. In comparison with patients with an RP sling, patients with a TOT sling have a higher incidence of persistent pain (32% versus 10%) and dyspareunia (18% versus 3%).[116] This finding is confirmed by a review and meta-analysis in which the rates of chronic groin and leg pain were higher in patients with a TOT sling compared with those of patients with an RP sling (16% versus 6.5%, respectively).[206]

Treatment of persistent pain in patients with a SMUS is particularly challenging and has been entirely empirical and progressive in nature. The treatment approach in these patients typically begins with pain medications and neuromodulatory medications such as carbamazepine, physical therapy or trigger-point injections and culminates with partial or complete mesh excision. Reported success rates of these treatments range from 24% to 100%,[9,40,43,107,277,312,326] but use of validated outcome measures documenting treatment success and long-term follow-up monitoring are both lacking. Furthermore, a number of case studies and series of patients with mesh complications have commented on the lifestyle-altering nature of painful complications in these patients.[9,40,107,312,326]

Fistulas

Urethrovaginal and vesicovaginal fistulas are rare SMUS-related complications, with a reported incidence of <1%.[46,48,66,98,173,178,212,217,334] These fistulas are most frequently associated with bladder or urethral erosion of the sling and patients can present in a variety of ways, and as late as 6 years after the initial surgery.[41,43,44,335–338] Despite their low reported incidence, the possibility of fistulas should be considered when patients present with recurrent incontinence, OAB, pain and/or voiding dysfunction after mesh surgery.[41] Not infrequently, a diagnosis of fistula can be obscured, owing to the presence of adjacent granulation tissue (Figure 4). Concurrent sphincteric incontinence might also confound diagnoses of fistulas,

especially in patients with a urethrovaginal fistula; thus, a careful evaluation should be undertaken to exclude fistula whenever a patient has recurrent incontinence after mesh sling surgery. This evaluation should include a physical examination with a stress test and visual confirmation that leakage is occurring through the urethral meatus as well as cystourethroscopy.[41] Surgical repair of urethral or vesicovaginal fistula requires the complete removal of all involved mesh and possible vaginal reconstruction with tissue flaps.[339] In patients with concomitant sphincteric incontinence, synchronous repair of a urethrovaginal fistula and an autologous fascial sling with a Martius flap interposed between the fistula repair and sling is often an effective treatment.[41,43]

Death

Mortality is the least common SMUS-related complication. In fact, in our literature review we did not find a single case series report that contains a postoperative death of a patient undergoing SMUS implantation surgery; However, In a study of bowel complications of SMUS, published in 2007,[133,] 7 deaths from bowel injuries after RP sling implantation were reported, and in 2014 another death after bowel perforation during a retropubic SMUS implantation was published as a case report.[132] Authors of a review of database entries regarding SMUS complications reported 10 deaths owing to bowel injury (six), vascular injury (three) and sepsis (one).[10] Authors of this study[10] suggested that death is an under-reported complication in patients treated with a SMUS.

Complications from mesh removal

Published reports on long-term outcomes of patients after mesh removal surgery are limited. All published studies are retrospective chart or database reviews and substantial heterogeneity exists in terms of both methodology and outcome measures.[9,41,43,44] Most authors of studies in this area commented on the technical difficulties encountered during mesh excision surgery and the fact that many (in some series, most) patients require two or more surgeries; thus, even in the short term, outcomes are often suboptimal.[6,9,40–45] Patients who underwent surgery with a primary indication of urethral obstruction had the highest success rates and those whose primary indication was pain had the least successful outcomes. Perioperative decision making is difficult in these patients and is often highly individualized, mostly based on the surgeon's experience and preferences: whether to attempt removal of all the mesh or just the suburethral or vaginal portions and whether to use a synchronous anti-incontinence or urethral reconstruction procedure.[9] Of note, in patients requiring mesh removal, recurrence of SUI has been reported in 10–60% of individuals.[9,43,78,84,85,94,100,138] An understanding of the possible outcomes of salvage surgery for mesh complications is critical in enabling accurate decisions regarding informed consent for the use of primary mesh surgery; however, few prospective or registry-based studies with published results currently exist that might address this need.[9,44,326]

Mesh–body Interactions

Despite the extensive use of polypropylene mesh dating back to the late 1950s,[340] in a variety of medical procedures, a paucity of data currently exists regarding the fate of this type of mesh once implanted in humans. Almost all of our knowledge of mesh–body interactions is derived from animal studies; explanted material from patients has been largely neglected as a source of information in this area. After >50 years of use, only a few published studies exist in which investigators actually examined histological changes in mesh explants that had been removed from humans.[35,341–343]

Despite this general lack of information, in one study of human explanted mesh samples and pathology records from 102 patients, <50% of explanted transvaginal mesh specimens were examined microscopically; however, when microscopy was performed, results of the microscopic examinations usually did not explain the specific complications experienced by the patients.[253] Several studies have confirmed this finding, noting that the assumption that mesh is widely considered to be biologically inert is based on results of short-term animal experiments without corroborating studies in humans.[342–344] At present, general human tissue interactions with the mesh are known, but we have an incomplete understanding of interactions specific to a mesh material and design as well as the pathophysiology of any complications.

Tissue responses to mesh

Inflammatory reactions

The inflammatory response to implanted mesh is nonspecific, similar to the foreign-body type of reaction initially described in the late 19th century.[345,346] However, only since the 1990s have tissue–implant interactions been studied, and, to date, few reports of the mechanisms involved have been published.[342–344] Immediately after implantation, foreign bodies, including modern implantable polymers, become coated with proteins followed by the appearance of inflammatory cells that migrate into the tissue, owing to the action of inflammatory mediators.[347,348] As in any tissue injury, the acute phase of inflammation is characterized by the appearance of short-lived neutrophils. Neutrophils are replaced within days by macrophages, which persist indefinitely. The initial phagocyte migration towards the foreign body does not seem to be driven by chemoattractants, but is dependent on the proteins, specifically fibrinogen, coating the implanted objects.[347,348] The macrophages then either persist and take on an epithelioid appearance or fuse to form multinucleated giant cells. Macrophage fusion occurs in the presence of certain cytokines, when the foreign object is too large to be phagocytosed by a single cell.[349] The macrophages are recruited in an attempt to destroy the foreign object and are the main component of the granulomatous inflammation triggered by the foreign body. The macrophages secrete an array of substances, such as bioactive lipids, hydrolytic enzymes, reactive oxygen metabolites and mediators of fibroblast proliferation.[350,351] In addition to

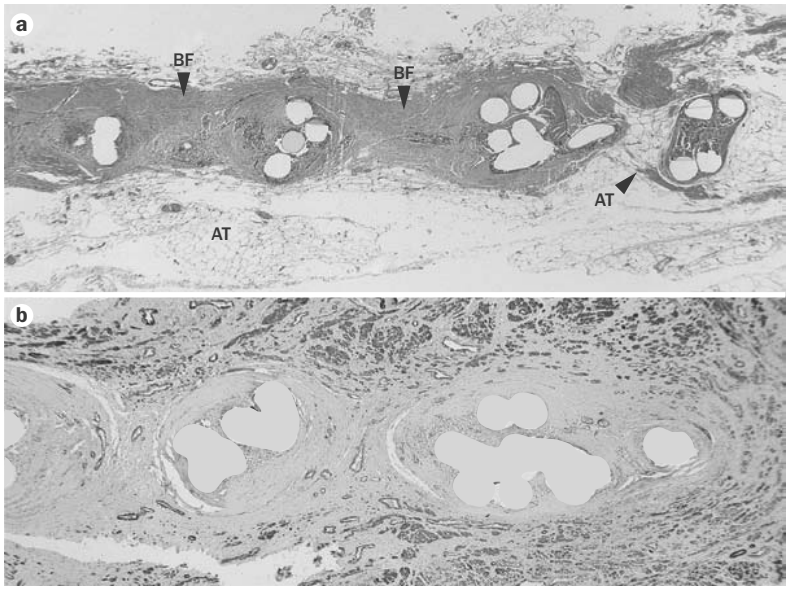


Figure 5 | Scar encapsulating mesh and surrounding pre-existent normal adipose and muscular tissues. **a** | ×2.5 image of a histological section showing a cross-section of mesh filaments as they appear in section, without colouring. Some filaments were labelled blue by the manufacturer. Adipose tissue had been present in the area before mesh placement. Tissue reaction to surgical injury and the mesh generated scar tissue encapsulating the mesh appears as dense pink collagenous tissue. The scar spans, or bridges, across mesh pores, which is termed bridging fibrosis. In this case a terminal pore contains nonscar adipose tissue (arrow with AT). This section has been labelled with a haematoxylin and eosin stain. **b** | ×2.5 image of a histological section showing cross-sections of mesh filaments. Note that the mesh is surrounded by a halo of fibrous tissue separating it from the pre-existent tissue of the vaginal wall, containing smooth muscle. Smooth muscle is labelled with anti α smooth muscle actin (brown), mesh filaments are filled yellow. The blue colour is a haematoxylin background stain. Abbreviations: AT, adipose tissue; BF, bridging fibrosis.

macrophage-mediated effects, a granulomatous reaction includes T lymphocytes as well as a smaller proportion of B lymphocytes and plasma cells. Each mesh filament ultimately becomes surrounded by a sheath of granulomatous inflammation and the entire mesh structure remains chronically inflamed.[342,352–354] Three clinically important aspects of mesh-induced inflammation exist: inflammatory mechanisms of pain, stimulation of fibrosis and polypropylene degradation.

Mesh integration

Mesh integration into the tissue is the result of wound repair mechanisms, which aim to restore tissue continuity. In most mammals after the foetal stage of development, the damaged tissue and void spaces are filled with fibrous, or scar tissue. This fibrous tissue functions as a nonspecific universal repair material or filler. In relation to implanted mesh, the body needs to repair tissue that was damaged during surgery, as well as fill the spaces within the mesh structure. The body also needs to repair the tissue damaged by mesh-associated inflammation.

With implanted mesh, granulomatous tissue inhabits the spaces within the mesh structure, such as the pores and interstices between mesh filaments; however, only provided the spaces are large enough to allow tissue ingrowth.[344] During the weeks after SMUS implantation, collagen deposits accumulate, while the fibroblasts acquire contractile filaments and transform into myofibroblasts. The contractile functions of these myofibroblasts together with reduction of extracellular fluid and collagen crosslinking results in wound contraction;[316,355] the overall aim of wound contraction being to minimize the volume of the maturing scar. In the scar-inhabiting mesh, the contractile forces act on the interlocked mesh–scar composite structure, which results in mesh contraction.[103,316,356] Maturation of the newly generated fibrous tissue is the next step in the repair process. During this maturation stage, collagen becomes increasingly organized and the density of the microvasculature recedes.[355]

Initially, the scar is composed of type III collagen, which is replaced by type I collagen as the scar matures. In the transition from type III to type I collagen, the structure is rearranged into cross-linked sheets that run parallel to tension forces.[355] The repaired area becomes a hypocellular scar that is then slowly remodeled, which can take ≥1 year to complete. Repeated or continuous damage to the tissue can cause the process of repair to be renewed at any stage. Thus, chronic inflammatory conditions can generate a large amount of scar tissue.

With foreign bodies such as mesh, the repair process is complicated by the inflammatory reaction, which is a stimulus for fibrosis. The amount of scar tissue that accumulates is dependent upon counterbalancing processes: stimulation, owing to the presence of a foreign body, and reduction of the scar volume by remodeling. In relation to implanted meshes, fibrous tissue fills the spaces within the mesh structure and surrounds the mesh.[342,343] The tissue then undergoes contraction and remodeling: the stimulus for fibrosis is, therefore, stronger around the mesh filaments and weaker far from the filaments, that is, in the mesh pores. Some larger pores might include fat or other components of normal connective tissue, while the surrounding filaments are fully encapsulated by the scar (Figure 4).[35] Bridging fibrosis can occur in the mesh, where the scar spans or bridges across the pores (Figure 5). Lightweight mesh designs containing pores of several millimetres in diameter have a greater chance of containing normal, nonscar connective tissue in the larger pores of their complex structures.[35,343] By contrast, heavyweight mesh designs, which are currently used for SMUS devices, lead to the development of a continuous scar plate, which encases all mesh filaments and spans across most of the pores (Figure 5).[35,343,357] Scar tissue also provides a connection between the composite mesh–scar structure and the surrounding normal tissue.

The process of healing also includes restoration of interrupted innervation and innervation of newly formed tissue. After mesh implantation the processes of reinnervation and/or neoinnervation are not overly affected by the presence of mesh.[34] Results of a study published in 2014, investigating samples from patients with inguinal hernia showed that the density of nerve branches in the scar encasing the mesh is similar to that of normal tissue

before surgery and marginally, but not significantly, lower than in the scar formed after non-mesh surgery.[34] In addition, nerve branches were observed in the interstices and pores of the mesh, probably growing through the mesh similar to small vessels that were observed to cross the mesh plane.[34] This finding indicates that tissues superficial to the mesh might be at least partially dependent on the through-the-mesh neurovascular supply (Figure 6).

Mesh degradation

The authors of several studies have reported degradation of polypropylene in explanted meshes;[36,341,358–361] however, the question of whether polypropylene degrades *in vivo* has not been fully resolved, despite decades of use.[37,362] Most conclusions of studies in this area were based on the observations of cracking on the exposed surfaces of explanted mesh filaments, which are usually examined using scanning electron microscopy.[351–353,355] The explanted tissue examined in these studies was typically fixed in formalin and had to be separated from the mesh using chemical reagents. Alternative hypotheses emerged that the cracking was either of residual biofilms or, if degradation occurred, it was induced by the formalin or cleaning reagents used. However, other studies demonstrated a similar appearance of polypropylene degradation occurring outside of the human body.[363–365] Before the publication of scanning electron microscopy studies of the mesh surface, authors of an earlier study, published in 1976, assessed the mechanical properties and molecular weight of implanted mesh and concluded that polypropylene degrades *in vivo*.[366] In this study, the investigators placed polypropylene implants with and without antioxidant subcutaneously in hamsters to determine the rate of degradation of the implant. They periodically removed specimens during a 5-month test period and analyzed the samples using infrared spectroscopy and dynamic mechanical testing.[363] The analyses showed that degradation began to occur after only a few days, although several factors suggested that the *in vivo* degradation process was similar to autoxidation that occurs in air or oxygen; in this study, the oxidation process was retarded through the use of an antioxidant.[363] A lack of published studies exists in this area, although the limited evidence suggests that implanted polypropylene undergoes a process of oxidative degradation, in which one of the factors is believed to be oxidative substances generated by macrophages.[366,367]

Effects of mesh on the tissue

Pain

Scar tissue inhabiting the mesh is not simply an inanimate filler, but a living tissue with its own vascular supply, innervation, fluid and acid–base balance mechanisms and immune response.[34,253,368] This tissue is subject to pain through normal mechanisms, caused by specific factors: persistent chronic inflammation, nerve ingrowth, tissue compartmentalization within the mesh and nonphysiological attachments to mobile tissues.

Inflammatory mediators cause hypersensitivity to everyday stimuli that leads to pain in response to touch or on movement and, if the stimulus is sufficiently high, can even lead to pain sensations at rest.[369] As discussed earlier, implantation of polypropylene meshes invariably results in an inflammatory response, which creates an environment capable of decreasing a patient's pain threshold (Figure 7).

The interlocking and compartmentalized nature is another specific feature of the mesh–scar complex. The ingrown tissue is in a vulnerable position, as it might be subjected to physical compression and distortion within the compartments of mesh pores and folds.[34] The risk of

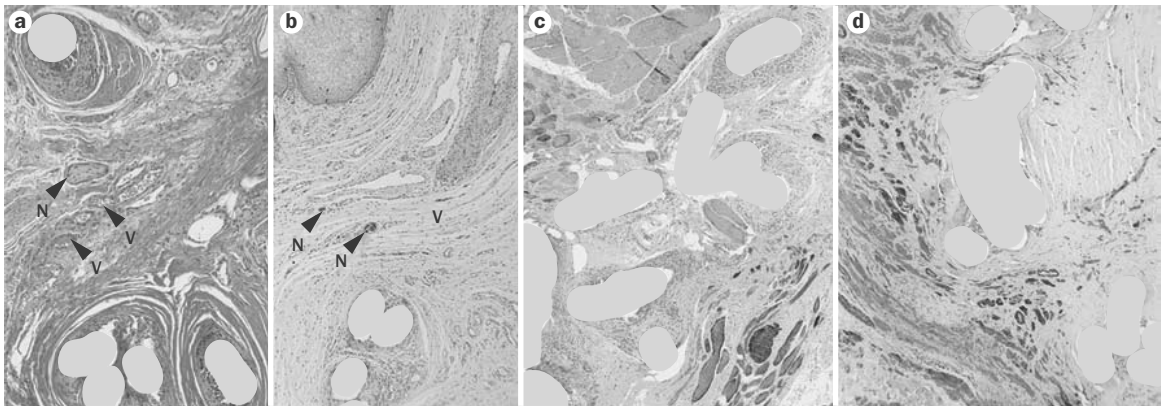


Figure 6 | Tissue interactions with explanted sling materials. **a**,**b** | ×10 images of a histological section showing a neurovascular bundle penetrating through a mesh pore. This section has been labelled with a haematoxylin and eosin stain. Cross sections of mesh filaments are filled yellow for demonstration purposes. The neurovascular bundle is within a mesh pore, orientated perpendicular to the mesh plane. **c** | ×10 image of a histological section showing muscle interposition between mesh filaments. This section has been anti-desmin-labelled (brown) to highlight the presence of striated muscle. Interlocked striated muscle is commonly observed in explanted transobturator tapes. **d** | ×10 image of a histological section showing α-smooth-muscle-actin-labelled smooth muscle from the vaginal wall, urethra or urinary bladder surrounding the sling material. Depending on the muscle origin, smooth muscle is likely to interact with mesh during physiological contractions (such as those that occur during urination or intercourse). Abbreviations: N, nerve branch; V, blood vessel.

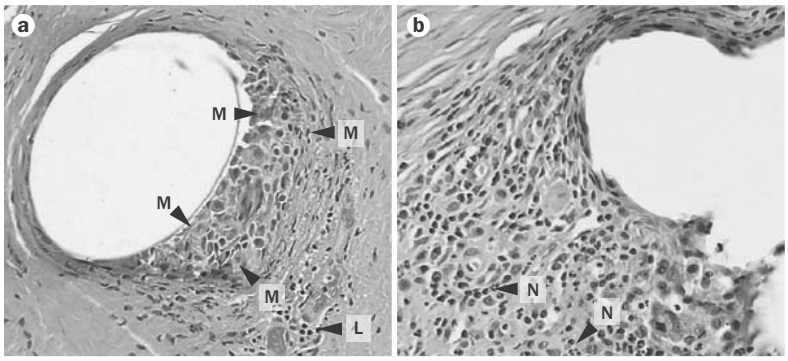


Figure 7 | Inflammatory reaction to the mesh. **a** | ×40 image of a histological section showing a cross-section of mesh filaments surrounded by foreign-body-type inflammation. Epithelioid macrophages (between arrows 'M'), which are the main component of granulomatous inflammation can be observed. A smaller number of lymphocytes ('L') can be seen seen surrounding the mesh filament. This section has been labelled with a haematoxylin and eosin stain. **b** | ×40 image of a histological section showing a cross-section of mesh filaments, characterized by the presence of neutrophils (multiple neutrophils are scattered in the infiltrate, two are labelled 'N' as examples). Acute inflammation is a feature of bacterial infection and is seen in patients with mesh exposure through the vaginal, urethral or bladder mucosa. Abbreviations: L, lymphocytes; M, macrophages; N, neutrophils.

compression might be a result of external forces, such as moving, bending and penile thrusting during intercourse, as well as a result of increased interstitial fluid pressure within the compartments. We have observed evidence of oedema within pores and deformation pockets (folds) of larger mesh devices indicating fluid imbalance within the mesh compartments (Figure 8). Externally, scar connection to the surrounding tissue might cause distortion and pulling during movement. These forces can act on the entire mesh structure, which in a SMUS has a long course compared with that of a hernia patch. This relatively long length of a SMUS might result in multiple sites of scar attachment to the tissues, which, in the case of TOT slings, includes actively contracting striated muscle.[277] These nonphysiological connections are subject to pulling forces that might induce pain, either as a result of muscle contraction or mobility during body movements. Additionally, mesh shrinkage during scar contraction might lead to static tension within and between attached tissues, also contributing to pain.[103]

Many authors have suggested nerve entrapment as a cause of SMUS-related pain. Entrapped nerves have been detected in mesh explants from patients with hernia,[34,35,370] and nerve branches have also been shown to grow into the mesh interstices in up to 90% of explanted mesh samples from patients with hernia.[34,35] Nerve entrapment has also been reported in patients fitted with a transvaginal mesh,[112] although few published studies exist in this area. In our unreported clinical experience of over 100 explanted mesh specimens, nearly all contained nerve branches of variable calibre (Figure 6). Interestingly, in patients undergoing hernia surgery, prophylactic neurectomy is offered as a method to reduce the incidence of pain after mesh repair.[371]

Some patients fitted with a SMUS report pain that is associated with specific movements or activities. The observation of interlocking of the mesh and striated muscle—resulting in muscle contraction and traction on entrapped nerves—offers a plausible hypothesis to explain this phenomenon in patients fitted with TOT slings. We have also observed interposition of smooth muscle, which might contribute to dyspareunia as the vaginal walls contract during intercourse (Figure 6).

Dyspareunia

Direct pressure and a wide range of tissue movement during sexual intercourse both pose additional risks to patients with a SMUS. The vaginal mucosa is one of the most densely innervated parts of the human body. Thus, if this mucosa overlies a stiffened mesh–scar structure, the nerve branches and receptors are subject to compression against the stiffened SMUS during intercourse. In addition, tissue movement on either side of the scar plate can cause traction and distortion of the mesh–scar structure. Findings of a study published in 2010[38] demonstrated the existence of a new complication unique to patients fitted with TOT slings, termed banding, which is a palpable firm scar in the paraurethral folds that was associated with dyspareunia in four of 12 sexually active women who were found to have banding on examination. Unfortunately, no data were presented describing the histopathology of excised tissue that was removed owing to painful banding, although little imagination is required to understand how this effect could cause pain (Figure 9).

Mesh exposure in the vaginal wall

Mesh erosion through the vaginal mucosa can result in a large variety of tissue responses, ranging from no detectable changes to substantial acute inflammation (Figure 7) and even formation of small abscesses. The dense acute inflammation almost always signifies bacterial infection.[372] From our unpublished experience, the site of mesh exposure also has a variable amount of granulated tissue. These changes correlate with the presenting symptoms, which range from no complaints to vaginal discharge, bleeding, dyspareunia and feeling of the exposed edge of the mesh by the sexual partner.

The mechanisms of mesh exposure and/or extrusion through the vaginal wall have not been well studied; however, an approximately 26-fold increase in vaginal and bladder exposure, extrusion or erosion when there had been a vaginal or bladder trocar perforation during the original surgery is known to exist.[31] Other risk factors have also been identified including patients' having undergone prior vaginal surgeries, larger incisions, smoking, diabetes mellitus of either type, pelvic exposure to radiation and older patient age.[96,124,321] The existence of these risk factors suggests that poor healing, lowered antibacterial immunity, insufficient vascularization, and scarring are all possible causes contributing to mesh exposure. In terms of mesh-specific factors, solid silicone strips or silicone-coated meshes have higher rates of erosion, indicating that choice of material

can affect the risk of vaginal mesh exposure.[105,373,374] Compared with other SMUS materials, silicone has limited adhesion to the tissues, which possibly enables more movement of the mesh, or tissue detachment. Patients fitted with a SMUS with a design that incorporates microporous materials with low tissue adherence, such as Gore-Tex® also have higher rates of mesh exposure through the vaginal wall,[375] compared with those of patients fitted with a SMUS that incorporates polypropylene mesh, which has larger pores.[301,356,376] In addition to the lower tissue adherence that enables mesh movement within the tissue, meshes with smaller pores do not allow tissue growth through the mesh. This lack of tissue growth likely interferes with vascularization and innervation of the overlying mucosa, which might lead to dystrophic changes and poor resistance to infection and necrosis.

Results of experiments conducted in animal models showed that the rate of mesh erosion was also dependent on the size of mesh implant, with animals implanted with larger mesh patches having a higher risk of exposure.[356,376] The higher exposure rate of larger mesh implants was likely a result of higher risks of mesh migration. Deformation was associated with the use of larger patches, more interference with vascularization and innervation of the overlying mucosa and the presence of larger volume of inflammation and/or fibrosis. Implantation with a smaller area of mesh might result in less risk of exposure, assuming that exposure is an entirely random event. In our unreported clinical experience of over 100 explanted polypropylene slings, we frequently observed that the exposed part of the explanted mesh was a curled edge piercing through the mucosa, suggesting that edge curling is also a mechanism of vaginal mesh exposure. In addition to the internal properties of a knitted structure, outward pressure of the tissue can act to curl the edge. Interestingly, resection of an exposed part of the mesh, either an edge or a mid-portion, leaves new edges that can also curl and become exposed. In our experience many mesh exposures, SMUS-related or implant-related pelvic organ prolapses recur after trimming of the exposed part.

Mesh migration

Mesh exposure through the vaginal wall seems to have several potential causes. Mesh erosion through the urethral or bladder mucosa reflects mesh migration (or incorrect SMUS placement). Mesh migration through the tissues and into the adjacent organs has been described when used in patients with hernia, in which two types of mesh migration have been suggested to occur: primary migration of unsecured mesh towards areas of least tissue resistance and secondary migration through transanatomical planes. The latter is facilitated by tissue forces acting to displace mesh while remodelling-induced and inflammation-induced tissue resorption enable this movement.[377,378] In patients with SMUS, mesh migration typically occurs into or through the urethral wall, which is a secondary type of migration.[9,10,39,41,326] Excessive tensioning of the sling can act to displace the mesh into the urethra, whereas an inflammatory reaction to a foreign body and the general ability of tissues to remodel under chronic pressures can enable mesh migration. Remnants of partially excised SMUS can potentially migrate in directions other than into the urethra.

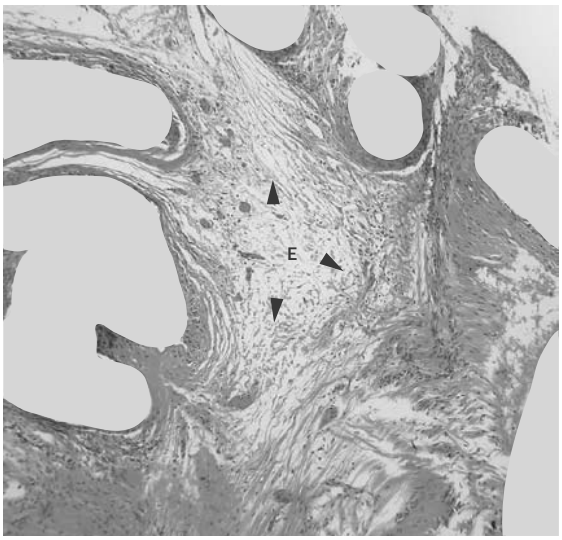


Figure 8 | Oedema within mesh compartments. ×20 image of a histological section showing ooedema in mesh compartments, note separation of collagen and low density of tissue in the area of the oedema (E). Oedema is usually seen in semi-enclosed mesh compartments. Mesh filaments are filled yellow in this image. This section has been labelled with a haematoxylin and eosin stain. Abbreviation: E, oedema

Mesh deformation

Mesh deformation, in which a part of mesh moves from its original or intended position, is related to mesh migration. In an *in vivo* study using white rabbits, Amid type I (Marlex®) meshes were found to be more likely to fold or curl at the edges in comparison to Amid type II meshes (Teflon®).[379] Similar to mesh migration, deformation can be primary, as a result of intraoperative or perioperative folding and edge curling of an unsecured mesh, or secondary, occurring after tissue ingrowth. Secondary wrinkling and folding of the mesh is attributed largely to mesh–scar contraction.[316] For transvaginal applications, folding and bunching of the mesh is frequently observed in patients with pelvic organ prolapse, who are often fitted with large devices, whereas mesh deformation of SMUS devices is typically limited to edge curling (Figure 9).[380] Edge curling of knitted mesh materials has been noticed following their surgical use in patients with hernia, where the edges can be secured by stitching; however, transvaginal devices have all edges unsecured. Narrow sling tapes might also show signs of fraying and curling of the edges when stretched. To address this risk of sling deformation, SMUS manufacturers have used heat treatment approaches, with variable degree of success.[381] As we note, rotation of a frayed edge towards the mucosa is another possible

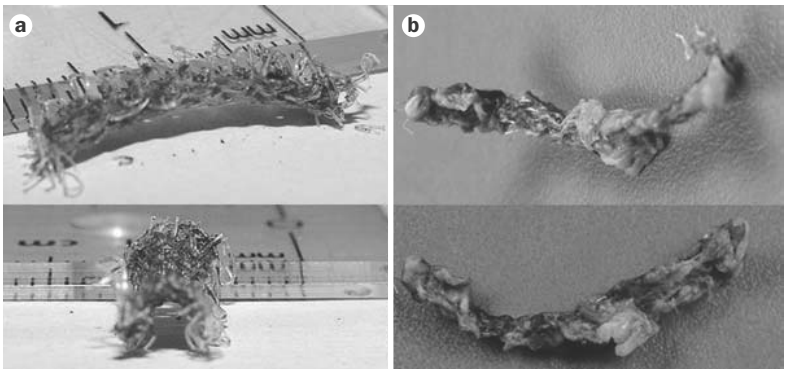


Figure 9 | Curling of the edges of explanted sling materials. **a** | Segment of a sling, which was explanted with very little adherent tissue and a structure that is readily visible. **b** | Segment of a mesh sling, which was excised with adherent tissue remaining attached to the sling material.

mechanism by which mucosal exposure of the mesh might take place.

Mesh stiffening

Elasticity and flexibility of knitted meshes is dependent on bending and movement of the mesh filaments. The extent of freedom of movement is often substantially reduced by the ingrowth of collagenous scar tissue. At the same time, the embedded mesh acts to reinforce the scar tissue, thus limiting native flexibility of the scar.[380,382–384] The resultant mesh–scar composite structure is stiffer than the original new mesh. The extent of the resultant increase in stiffness is dependent on mesh design, including the physical characteristics of the material and the amount of induced fibrous scar.[294,316,382–384] For SMUS devices, excessive tightening and connection to the surrounding tissues might limit mobility and add to the structural stiffness. This phenomenon has been observed in the clinic, where it is referred to as 'banding'.[38] Mesh stiffening is likely to occur owing to degradation of polypropylene, as the degraded layer often shows embrittlement.[357–359,361,366] This component of stiffening is expected to increase over time.

Urinary symptoms

SMUS are designed to support the urethra; however, as discussed previously, the amount of pressure can become excessive owing to mesh contraction and reduction of the area of support. A stretched mesh has a reduced width, which, together with edge curling has been described as 'roping' (Figure 9).[385] A stiffened, over-tightened sling, therefore, has limited elasticity and cannot accommodate a full range of changes in tension. SMUS tension changes dynamically during cough, sexual intercourse and other physiological processes, which adds to the static pressure on the urethra. The result is urinary retention and transmigration of the mesh into, or through the urethral wall. Interestingly, mesh removal does not necessarily lead to recurrent SUI.[369,370] This finding suggests that scarring around the mesh, which remains after mesh explantation, is sufficient to maintain continence in some patients.

Polypropylene degradation products

The breakdown of mesh is expected to result in the presence of small molecular complexes and chemical products of degradation, as is the case for any polymerized hydrocarbon. *In vitro* thermal degradation of polypropylene at high temperatures produces an array of organic molecules such as acids, ketones, ethers, aldehydes, alcohols and smaller hydrocarbons.[386] The *in vitro* conditions required for thermal degradation, however, are different to those observed under *in vivo* conditions, and we are not aware of any studies that either simulated body conditions or conducted chemical analysis of explanted tissue. An assumption can be made that, to some extent, any combination of the degradation products detected during thermal or other types of degradation can be produced in the tissue. Additionally, additives used to stabilize the polymer might theoretically leach into the surrounding tissue.

Accumulations of polypropylene degradation products are expected to be confined within the scar capsule and have more local, rather than systemic, effects on the body, owing to their fibrous encapsulation; however, no published studies currently address this point. The degradation products might act as an additional stimulus for the chronic inflammatory response. Accumulation and toxicity of these degradation products might cause tissue damage and contribute to the continuous remodelling around the mesh filaments and extension of fibrosis.[387]

Tumorigenicity

Three cases of cancer that might be associated with implanted polypropylene mesh have been reported in humans. Two patients had squamous cell cancers 6 years and 22 years after mesh hernia repairs, respectively;[388] in addition, an inflammatory myofibroblastic tumour following implantation of an RP sling has also been reported.[384] In the patients who had mesh hernia repairs, both had a complicated clinical course involving chronic mesh exposure and infection.[383] Chronic skin wounds are an established risk factor for squamous cell carcinoma. The one known patient with an RP-sling-related tumour had a myofibroblastic neoplasm with local recurrence potential, which is considered an intermediate state between a benign tumour and sarcoma. Potential risks of tumorigenesis in patients with SMUS include chronic mucosal erosions, chronic inflammation surrounding the mesh and the possible presence of degradation products and polypropylene additives released into the tissue. Mutagenic effects, in general can take many years to accumulate and then a long period to cause a neoplasm. Detecting any oncogenic effects of SMUS implants would require a large cohort of patients with the same type of implant, and these patients would have to be followed up for a sufficiently long period of time, most likely at least 15 years. The long-term use of hernia meshes has not revealed a significant oncogenic risk; however, the constant introduction of new mesh designs further complicates investigations of mesh-related cancer risks, as these new

designs probably vary in terms of the chemical composition of the polypropylene used. In general, based on our knowledge of tumorigenesis, three tissue types might be affected by introduction of a SMUS: epithelium; soft tissue; and lymphocytes, which could result in malignant transformation into carcinoma, sarcoma and lymphoma, respectively.

As described, a small risk of developing squamous cell carcinoma associated with chronic mesh exposure has been reported in patients with hernia meshes.[388] In transvaginal applications of similar materials, chronic erosions might, therefore, increase the risk of squamous cell carcinoma. The importance of concurrent local infections with high-risk variants of human papillomavirus needs to be studied, as these might have a synergistic effect in increasing a patient's cancer risk.

Carcinogenic effects of polypropylene, specifically leading to the development of sarcomas, have been studied in animal models. In rodents, implantation with flat polypropylene plates resulted in higher tumorigenicity than placement of porous materials.[389] A study of implanted polypropylene meshes in mice concluded that the risk of carcinogenesis following mesh implantation, if existent, is not immediate; however the follow-up duration of this study was only 2 years.[390] Another group of researchers implanted transponders made of polypropylene into carcinogen-sensitive *p53*$^{\pm}$ transgenic mice and observed development of sarcomas in 10% of animals within 6 months of exposure.[391] Other reports have corroborated these findings.[392–394] The basic research and clinical data suggest that implantation of polypropylene mesh might increase the risk of sarcoma, however if a risk is present in humans it is likely to be very low.

A potential risk of lymphoma needs to be considered in patients with any prosthetic implants, including SMUS, as this effect has been well documented in women with breast implants.[395,396] The exact aetiology of lymphoma owing to breast implants is not presently known, and this increased risk was detected in association with either saline or silicone implants. The increased risk of lymphoma might be related to an inflammatory reaction to the implants, rather than to the material of the devices; therefore, this risk might also be relevant to a large range of other implants that induce inflammatory responses, including SMUS. The large size of breast implants relative to most other implanted materials and the high volume of use for over 30 years might explain why this small, specific risk became detectable. Whether or not the same risk exists in patients with SMUS is currently unknown. In women with breast implants, the average time between implantation and a diagnosis of lymphoma is reported to be 9 years (range 1–32 years).[396]

Conclusion

In the words of the astronomer Carl Sagan—"The absence of evidence is not evidence of absence".[397] With respect to the safety of sling surgery, the lack of good studies about the incidence and severity of SMUS complications is not evidence that these complications are uncommon, nor is it evidence that they are not serious. The effectiveness of synthetic slings remains unchallenged, although, as this Review documents, an increasing body of evidence exists that serious and sometimes lifestyle-altering complications are underreported and underappreciated by doctors and patients alike. The true incidence of SMUS-related complications is unknown, owing, in no small part, to the poor overall quality of the studies. Nevertheless, we have calculated the minimum risks: revision surgery for erosion and obstruction alone, 5.6%; chronic pain, 4.3%; recurrent or persistent SUI, 5.3%; and *de novo* refractory OAB 3.9% (Box 1). These data are not mutually exclusive, although we calculated the overall risk of a serious complication or surgical failure to be 12.5%. We emphasize, though, that these data represent the absolute minimum rate of complications reported in the literature; the actual rate might be considerably higher.

Urologists can and must do better in assessing the long-term safety of SMUS surgery and in developing better methods of monitoring patients and assessing the outcomes of treatment for complications, so that both patients and physicians can be advised of the true risks associated with a SMUS.

Review criteria

A systematic review of the English language literature was performed in August 2014 to investigate the published efficacy, effectiveness and complications of SMUS. The search used a complex search strategy of the Medline database, including medical subject heading (MeSH) and free-text protocols. The MeSH search combined the terms "mid urethral sling", "midurethral sling", "suburethral sling", "urethral sling", "mid urethral slings", "midurethral slings", "suburethral slings", "urethral slings" and "follow-up study". Multiple free-text searches included the terms "Urinar*incont*", "TVT", "tension-free vaginal tape*", "Tension-free vaginal sling*", "Transobturator tape*", "Transobturator sling*", "TVT-obturator", "TVT-O", "TVT secure", "miniarc", "abbrevio", "TOT", "suprapubic arc sling*", "SPARC sling*", "intravaginal slingplasty", "IVS sling", "Raz sling", "Uratape", "ObTAPE", "Prepubic sling*", "Prepubic TVT", "Prepubic tape*", "PelviLace", "Ureter", "Aris", "In-Fast", "Monarc", "I-Stop", "urethral reconstruction", "urethrovaginal fistula", "Obtape", "gortex sling", "silastic sling", "mersilene sling", "marlex sling", "vesicovaginal fistula", "BioArc" individually in the fields title and abstract of the records. Subsequently, the search was limited to only human patients. A total of 995 records were retrieved from Medline, 249 were included. Six of the authors reviewed the full texts to select relevant papers. Discrepancies were solved by open discussion. Once the citations were accrued and the papers read, the bibliographies were cross-checked for any relevant citations that were missed in the initial search, which totalled an additional to 88 articles. Only articles published since 2007 were included in the reporting of complications to update and expand upon a review published in 2008.[334] For the section on mesh–body interactions, the search was not limited to humans nor was there a limit on publication date.

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Author contributions

All authors made a researched data for this article, J.G.B., M.S.B., G.M., R.B. and V.I. contributed to discussions of content, J.G.B., R.S.P., M.S.B., G.M., R.B. and V.I. wrote the manuscript and J.G.B., R.S.P., M.S.B., R.B. and V.I. made a substantial contribution to reviewing and/or editing of this manuscript prior to submission.